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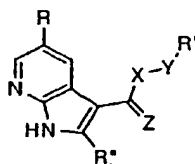
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(54) Title: 7-AZAINDOLES AS INHIBITORS OF C-JUN N-TERMINAL KINASES FOR THE TREATMENT OF NEURODE-
GENERATIVE DISORDERS



(I)

(57) Abstract: The present invention relates to novel 3,5-substituted 7-azaindole compounds of formula (I), their use in the inhibition of c-Jun N-terminal kinases, their use in medicine and particularly in the prevention and/or treatment of neurodegenerative disorders related to apoptosis and/or inflammation. The invention also provides processes for manufacture of said compounds, compositions containing them and processes for manufacturing such compositions.

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7-AZAINDOLES AS INHIBITORS OF C-JUN N-TERMINAL KINASES FOR THE TREATMENT OF NEURODEGENERATIVE DISORDERS

- 5 The present invention relates to novel 3,5-substituted 7-azaindole compounds, their use in the inhibition of c-Jun N-terminal kinases, their use in medicine and particularly in the prevention and/or treatment of neurodegenerative disorders related to apoptosis and/or inflammation. The invention also provides processes for manufacture of said compounds, compositions containing them and processes for manufacturing such compositions.
- 10 c-Jun N-terminal kinases (hereinafter referred to as "JNKs") are members of the mitogen-activated protein kinase (MAPK) family. JNKs are involved in response to various stimuli, including proinflammatory cytokines and environmental stress. JNKs, and JNK3 in particular, play an important role during apoptotic death of cells and therefore have been implicated in various
- 15 disorders including stroke, traumatic brain injury and other neurodegenerative diseases such as Parkinson disease, Alzheimer disease and others. Since JNK activity is a physiological regulator of AP-1 transcriptional activity, JNK inhibitors are expected to reduce inflammatory response.
- 20 Apoptosis is a form of cell death in which the cell actively participates in its own destruction in a process involving a characteristic series of biochemical and morphological changes which are regulated by specific cell death genes. The apoptotic cell death is a process that has been observed in the developing mammalian nervous system. In mice, the inactivation by homologous
- 25 recombination of genes that encode proteins that promote apoptosis, such as the caspase-3 or the Bax protein, prevents developmental neuronal cell death. The destruction of genes that encode cell death suppressors such as Bcl-x, leads to enhanced neuronal cell death. There is increasing evidence that apoptosis plays an important role in the pathology of acute and chronic neurodegenerative
- 30 diseases. For example, in transgenic mice overexpressing the anti-apoptotic Bcl-2 protein in the nervous system there is a decrease in infarct volume following cerebral ischemia. Similarly, injection of the caspase inhibitor BAF reduces neuronal cell death following hypoxia/ischaemia in neonatal rats. Another

example is spinal muscular atrophy (a motor neurondisease) where loss of function mutations in the SMN gene is associated with the disease. Recent data has shown that the wild type SMN protein binds to Bcl-2 and co-operates with it to inhibit apoptosis. These results suggest that inhibitors of neuronal apoptosis could be beneficial in the treatment of human neurodegenerative diseases. There is increasing evidence that neuronal apoptosis is an important pathological feature of stroke, traumatic brain injury and other neurodegenerative diseases. Therefore, pharmacotherapy using inhibitors of neuronal apoptosis may provide a therapeutic benefit in neurodegenerative conditions.

A number of groups have studied the mechanisms of neuronal cell death using *in vitro* cell culture systems and the results suggest that in some systems the transcription factor c-Jun is activated by the removal of survival signals and promotes cell death.

Antibodies specific for c-Jun protected NGF-deprived rat sympathetic neurones from apoptosis. Analogous neuroprotection due to expression of a c-Jun dominant negative mutant has been demonstrated, whereas overexpression of wild type c-Jun protein was sufficient to induce apoptosis in the presence of NGF. Estus and co-workers recently showed that an increase in c-Jun RNA levels occurs in cortical neurones undergoing apoptosis after treatment with β -amyloid peptide (Estus *et al.*, 1997, J. Neurosci. 17, 7736-7745). It has also been shown that c-Jun is required for apoptosis in cerebellar granule neurones deprived of survival signals.

c-Jun is activated by JNKs, which phosphorylate its transcriptional activation domain. In humans there are three JNK genes : JNK1, JNK2 and JNK3. The RNAs encoding JNK1 and JNK2 are expressed in many tissues, including the brain, but JNK3 is restricted to the nervous system and to a smaller extent the heart and testes.

JNKs are strongly activated in cellular responses to various stresses such as UV radiation, heat shock, osmotic shock, DNA-damaging agents, and

proinflammatory cytokines such as $\text{TNF}\alpha$, $\text{IL-1}\beta$ and others. Upstream regulators of the JNK pathway include kinases such as SEK1, MKK7 and MEKK1. There is evidence that Jun kinase activity is required for neuronal apoptosis *in vitro*. Overexpression of MEKK1 in sympathetic neurones increased c-Jun protein levels and phosphorylation and induced apoptosis in the presence of NGF indicating that activation of the Jun kinase pathway can trigger neuronal cell death. The Jun kinase pathway has been shown to be necessary for the death of differentiated PC12 cells deprived of NGF. Furthermore, compound CEP-1347, which inhibits the c-Jun pathway (upstream of Jun kinase), protects motor neurones against cell death induced by survival factor withdrawal.

In JNK3 homozygous (-/-) knockout mice, epileptic seizures and death of hippocampal CA3 neurones induced by injection of kainic acid is blocked. This indicates that JNK3 is involved in certain forms of neuronal cell death *in vivo*. It is also a critical component of GluR6-mediated excitotoxicity. Furthermore, JNK3 (-/-) mice appear to develop normally and are viable suggesting that JNK3 is not essential for development or viability.

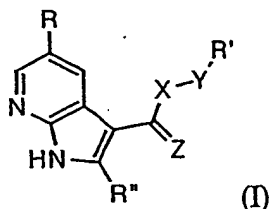
Strong nuclear JNK3 immunoreactivity in the brain CA1 neurones of patients with acute hypoxia suggests that JNK3 is involved in hypoxia-related neurodegeneration. Transient hypoxia, may also trigger apoptosis through JNK signaling pathway in developing brain neurones.

Furthermore, JNK3 immunoreactivity is colocalized with Alzheimer disease-affected neurones. Moreover JNK3 is related to neurofibrillary pathology of Alzheimer disease. In particular, JNK3 induces robust phosphorylation of amyloid precursor protein (APP) thus affecting its metabolism in disease state.

The present inventors have provided compounds which are inhibitors of c-Jun N-terminal kinases.

The present invention relates to a compound of formula (I) as defined below

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wherein

5 R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

10 each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R²,
 15 COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined below and wherein:

the C₁₋₁₂ alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O)₂- wherein each R² may be the same or different and is as defined below;

the C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R²; wherein each R² may be the same or different and is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C₁₋₁₂ alkyl,

each saturated carbon in the optional fused ring is further optionally and independently substituted by $=O$, $=S$, $=NNHR^2$, NNR^2R^2 , $=N-OR^2$, $=NNHCOR^2$, $=NNHCO_2R^2$, $=NNSO_2R^2$, or $=NR^2$, wherein each R^2 may be the same or different and is as defined below; and

5 each substitutable nitrogen atom in R is optionally substituted by R^3 , COR^2 , SO_2R^2 or CO_2R^2 , wherein each R^2 and R^3 may be the same or different and is as defined below;

R^2 is hydrogen, C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4 , SR^4 , NO_2 , CN , NR^4R^4 , NR^4COR^4 , $NR^4CONR^4R^4$, NR^4COR^4 , $NR^4CO_2R^4$, CO_2R^4 , COR^4 , $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, $SO_2NR^4R^4$, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of $-O-$, $-N(R^4)-$, $-S(O)-$ and $-S(O_2)-$, wherein each R^4 may be the same or different and is as defined below;

15 R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4 , SR^4 , NO_2 , CN , NR^4R^4 , NR^4COR^4 , $NR^4CONR^4R^4$, NR^4COR^4 , $NR^4CO_2R^4$, CO_2R^4 , COR^4 , $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, $SO_2NR^4R^4$, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of $-O-$, $-N(R^4)-$, $-S(O)-$ and $-S(O_2)-$, wherein each R^4 may be the same or different and is as defined below;

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

25 R' is C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, carbocyclyl or heterocyclyl, each of which is optionally substituted, wherein:

the optionally substituted carbocyclyl or heterocyclyl group is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered rings containing zero to three heteroatoms,

30 each substitutable carbon atom in R' , including the optional fused ring, is optionally and independently substituted by one or more of C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, aryl, heteroaryl halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN , NR^2R^2 ,

NR^2COR^2 , $\text{NR}^2\text{CONR}^2\text{R}^2$, NR^2COR^2 , $\text{NR}^2\text{CO}_2\text{R}^2$, CO_2R^2 , COR^2 , CONR^2R^2 , $\text{S(O)}_2\text{R}^2$, SONH_2 , S(O)R^2 , $\text{SO}_2\text{NR}^2\text{R}^2$, $\text{NR}^2\text{S(O)}_2\text{R}^2$, wherein each R^2 may be the same or different and is as defined above and wherein:

- 5 the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of $-\text{O}-$, $-\text{C(O)}-$, $-\text{N(R}^2)-$, $-\text{S(O)}-$ and $-\text{S(O)}_2-$, wherein each R^2 may be the same or different and is as defined above;
- 10 the C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one or more of halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN , NR^2R^2 , NR^2COR^2 , $\text{NR}^2\text{CONR}^2\text{R}^2$, NR^2COR^2 , $\text{NR}^2\text{CO}_2\text{R}^2$, CO_2R^2 , COR^2 , CONR^2R^2 , $\text{S(O)}_2\text{R}^2$, SONH_2 , S(O)R^2 , $\text{SO}_2\text{NR}^2\text{R}^2$, $\text{NR}^2\text{S(O)}_2\text{R}^2$, wherein each R^2 may be the same or different and is as defined above; and
- 15 the C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one or more C_{1-12} alkyl groups;
- 20 each saturated carbon in R' , including the optional fused ring, is further optionally and independently substituted by $=\text{O}$, $=\text{S}$, NNR^2R^2 , $=\text{N-OR}^2$, $=\text{NNHCO}_2\text{R}^2$, $=\text{NNHCO}_2\text{R}^2$, $=\text{NNSO}_2\text{R}^2$, or $=\text{NR}^2$, wherein each R^2 may be the same or different and is as defined above; and
- 25 each substitutable nitrogen atom in R' is optionally substituted by R^3 , COR^2 , SO_2R^2 or CO_2R^2 wherein each R^2 and R^3 may be the same or different and is as defined above;

R'' is hydrogen, C_{1-12} alkyl, carbocyclyl or heterocyclyl, each of which is optionally substituted, wherein:

- 30 the said carbocyclyl or heterocyclyl is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

each substitutable carbon atom in R'', including the optional fused ring, is optionally and independently substituted by one or more of C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, heteroaryl, halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂ NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined below and wherein:

the C₁₋₁₂ alkyl group optionally incorporate one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O₂)-;

the C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, and heteroaryl groups are optionally substituted by one or more of halogen, haloalkyl, unsaturated or partly saturated cycloalkyl, aryl, or heteroaryl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂ NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined above; and

the C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, and heteroaryl groups, are optionally substituted by one or more C₁₋₁₂ alkyl

each saturated carbon in R'', including the optional fused ring, is further optionally and independently substituted by =O, =S, NNR²R², =N-OR², =NNHCOR², =NNHCO₂R², =NNSO₂R², or =NR², wherein each R² may be the same or different and is as defined above; and

each substitutable nitrogen atom in R'' is optionally substituted by R³, COR², SO₂ R² or CO₂ R², wherein each R² and R³ may be the same or different and is as defined above;

X is NR⁵; O, S or C₁₋₄ alkylene that is optionally substituted by one or more of halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR²,

$\text{NR}^2\text{CONR}^2\text{R}^2$, NR^2COR^2 , $\text{NR}^2\text{CO}_2\text{R}^2$, CO_2R^2 , COR^2 , CONR^2R^2 , $\text{S(O)}_2\text{R}^2$, SONH_2 , S(O)R^2 , $\text{SO}_2\text{NR}^2\text{R}^2$, $\text{NR}^2\text{S(O)}_2\text{R}^2$, wherein each R^2 may be the same or different and is as defined above and R^5 is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkyl; and

5

Y is absent or is NR^6 , O, CR^6R^6 , or C_{1-4} alkylene wherein each R^6 may be the same or different and is H, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} haloalkyl; and

10

Z is O, S or NR^7 wherein each R^7 may be the same or different and is hydrogen, C_{1-4} alkyl optionally substituted with one or more of halide, OR^8 , NR^8R^8 or aryl, where R^8 is independently H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy;

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and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, including esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents or prodrugs thereof.

20

For the avoidance of doubt, when a group as defined above contains two or more radicals, e.g. the radical R^2 , as for example in the groups $\text{SO}_2\text{NR}^2\text{R}^2$ and NR^2COR^2 , the radicals R^2 may be the same or different.

25

For the purposes of this invention, "alkyl" means a straight chain or branched alkyl radical of 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms and most preferably 1 to 4 carbon atoms including but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl etc. The term "alkenyl" means a straight chain or branched alkylenyl radical of 2 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon double bonds and includes but is not limited to ethylene, n-propyl-1-ene, n-propyl-2-ene, isopropylene, etc. The term "alkynyl" means a straight chain or branched alkynyl radical of 2 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon triple bonds and includes but is not

30

limited to ethynyl, 2-methylethynyl etc. The term "cycloalkyl" means an saturated or partly unsaturated 3-12 membered cyclic alkyl group and includes but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl etc. Cycloalkyl groups may be optionally substituted or fused to one or more aryl,
5 heterocyclyl or cycloalkyl group. "Heterocycloalkyl" means a 3-12 membered saturated or partly unsaturated cycloalkyl containing one or more hetero atom selected from N, S and O. "Haloalkyl" means an alkyl radical substituted with one or more halide atoms for example $\text{CH}_2\text{CH}_2\text{Br}$, CF_3 or CCl_3 .

10 "Carbocyclyl" relates to a saturated, partly unsaturated or unsaturated 3-10 membered hydrocarbon ring, including cycloalkyl and aryl.

"Aryl" means an aromatic 3-10 membered hydrocarbon containing one ring or being fused to one or more saturated or unsaturated rings including but not
15 limited to phenyl, naphthyl, anthracenyl or phenanthracenyl.

"Heteroaryl" means an aromatic 3-10 membered aryl containing one or more heteroatoms selected from N, O or S and containing one ring or being fused to one or more saturated or unsaturated rings and.

20

"Heterocyclyl" means a 3-10 membered ring system containing one or more heteroatoms selected from N, O or S and includes heteroaryl. The heterocyclyl system can contain one ring or may be fused to one or more saturated or unsaturated rings; the heterocyclyl can be fully saturated, partially saturated or
25 unsaturated and includes but is not limited to heteroaryl and heterocarbocyclyl, e.g. cyclohexyl, phenyl, acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, carbazole, cinnoline, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline,
30 isoxazole, isothiazole, morpholine, naphthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine,

pyrrole, pyrrolidine, pyrroline, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane;

5

Halogen means F, Cl, Br or I, preferably F.

10

Preferably, R is an aryl or a heteroaryl radical, optionally substituted with one or more of alkyl, haloalkyl, halogen, OR^2 , SR^2 , SOR^2 , $(NR^2)_2$, wherein R^2 is independently selected from hydrogen, C_{1-4} alkyl or haloalkyl. More preferably R is aryl, more preferable phenyl or naphthyl, most preferably phenyl; the heterocyclyl group is preferably furanyl, thiophenyl, pyridyl or quinolinyl. If R is phenyl, it is preferably substituted in the 3-(meta) position or the 4-(para) position.

15

When R is substituted, the preferred substituent is F, Cl or Br, more preferably F; or haloalkyl, preferably CF_3 , or alkyl, preferably methyl, ethyl or propyl. Most preferably, R is 3-fluorophenyl.

20

R' is preferably C_{1-4} alkyl, alkenyl or alkynyl, especially when Y stands for an alkylene group. R' may also stand for aryl, preferably phenyl, or a heteroaryl containing up to 3 hetero atoms, or a cycloalkyl or heterocycloalkyl group, each of which may be fused to one or more aryl, heteroaryl, cycloalkyl or heterocycloalkyl rings, each optionally substituted by one or more of alkyl, halide or alkoxy.

25

R'' is preferably H, C_{1-4} alkyl (e.g. methyl, ethyl or propyl), aryl, heteroaryl, cycloalkyl or heterocycloalkyl. R'' is most preferably H.

30

X is preferably NR^5 , most preferably NH, or a straight chain or branched C_{1-4} alkylene and preferably methylene or ethylene;

Y is preferably either absent or a straight or branched chain C₁₋₄, e.g. methylene or methylenemethylene, or NH especially when X stands for NR⁵.

Z is preferably O.

5

Preferably aryl is phenyl or naphthyl; alkylaryl is preferably methyl or ethyl carrying one or more phenyl groups (for example -CH₂Ph or -C(Ph)₃) wherein the aryl group may be substituted by any of the substituents discussed above e.g. methoxy; heterocyclyl is preferably 2-pyridyl, 4-pyridyl, 2-quinolinyl, 2-pyrimidinyl, pyrazinyl, 2-quinoxaliny, 1-isoquinolinyl or 4-quinolinyl, more
10 preferably 2-pyridyl or 4-pyridyl, the cycloalkyl group is a 3, 4, 5, 6 or 7 membered ring and can be fused to one or more aryl, heterocyclyl or cycloalkyl group.

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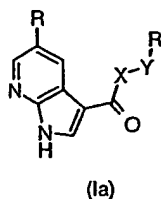
Preferably phenyl groups are substituted with halogen, alkyl, haloalkyl, aryl alkylaryl, NO₂, NH₂ or alkoxy; preferably naphthyl groups are optionally substituted with alkyl more preferably with methyl; preferably heterocyclyl groups are optionally substituted with haloalkyl, alkyl, CN or alkoxy.

20

Preferably halogen is F, Cl or Br; alkyl is preferably methyl, ethyl, propyl or butyl; haloalkyl is preferably CF₃.

In a preferred feature of the first aspect, there is provided a compound of formula (Ia) as defined below;

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wherein

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R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

5 each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R²,
10 wherein each R² may be the same or different and is as defined below and wherein:

the C₁₋₁₂ alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O)₂- wherein each R² may be the same or different and is
15 as defined below;

the C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R²; wherein each R² may be the same or different and
20 is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C₁₋₁₂ alkyl,

each saturated carbon in the optional fused ring is further optionally and
25 independently substituted by =O, =S, =NNHR², NNR²R², =N-OR², =NNHCOR², =NNHCO₂R², =NNSO₂R², or =NR², wherein each R² may be the same or different and is as defined below; and

each substitutable nitrogen atom in R is optionally substituted by R³, COR², SO₂R² or CO₂R², wherein each R² and R³ may be the same or
30 different and is as defined below;

R² is hydrogen, C₁₋₁₂ alkyl or aryl, optionally substituted by one or more of C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, OR⁴, SR⁴, NO₂, CN, NR⁴R⁴, NR⁴COR⁴, NR⁴CONR⁴R⁴, NR⁴COR⁴, NR⁴CO₂R⁴, CO₂R⁴, COR⁴,

CONR⁴₂, S(O)₂R⁴, SONH₂, S(O)R⁴, SO₂ NR⁴R⁴, NR⁴S(O)₂R⁴, wherein the C₁₋₁₂ alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R⁴)-, -S(O)- and -S(O₂)-, wherein each R⁴ may be the same or different and is as defined below;

5 R³ is C₁₋₁₂ alkyl or aryl, optionally substituted by one or more of C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, OR⁴, SR⁴, NO₂, CN, NR⁴R⁴, NR⁴COR⁴, NR⁴CONR⁴R⁴, NR⁴COR⁴, NR⁴CO₂R⁴, CO₂R⁴, COR⁴, CONR⁴₂, S(O)₂R⁴, SONH₂, S(O)R⁴, SO₂ NR⁴R⁴, NR⁴S(O)₂R⁴, wherein the C₁₋₁₂ alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R⁴)-, -S(O)- and -S(O₂)-, wherein each R⁴ may be
10 the same or different and is as defined below;

R⁴ is hydrogen, C₁₋₄ alkyl, or C₁₋₄ haloalkyl;

15 R' is C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, carbocyclyl or heterocyclyl, each of which is optionally substituted, wherein:

the optionally substituted carbocyclyl or heterocyclyl group is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered rings containing zero to three heteroatoms,

20 each substitutable carbon atom in R', including the optional fused ring, is optionally and independently substituted by one or more of C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, heteroaryl halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR²,
25 CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂ NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined above and wherein:

the C₁₋₁₂ alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O₂)-, wherein each R² may be the same or different and is as defined above;

30 the C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one

5 or more of halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN , NR^2R^2 , NR^2COR^2 , $NR^2CONR^2R^2$, NR^2COR^2 , $NR^2CO_2R^2$, CO_2R^2 , COR^2 , $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$, wherein each R^2 may be the same or different and is as defined above; and

the C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one or more C_{1-12} alkyl groups;

10 each saturated carbon in R' , including the optional fused ring, is further optionally and independently substituted by $=O$, $=S$, NNR^2R^2 , $=N-OR^2$, $=NNHCOR^2$, $=NNHCO_2R^2$, $=NNSO_2R^2$, or $=NR^2$, wherein each R^2 may be the same or different and is as defined above; and

each substitutable nitrogen atom in R' is optionally substituted by

15 R^3 , COR^2 , SO_2R^2 or CO_2R^2 wherein each R^2 and R^3 may be the same or different and is as defined above;

20 X is NR^5 ; O, S or C_{1-4} alkylene that is optionally substituted by one or more of halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN , NR^2R^2 , NR^2COR^2 , $NR^2CONR^2R^2$, NR^2COR^2 , $NR^2CO_2R^2$, CO_2R^2 , COR^2 , $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$, wherein each R^2 may be the same or different and is as defined above and R^5 is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkyl; and

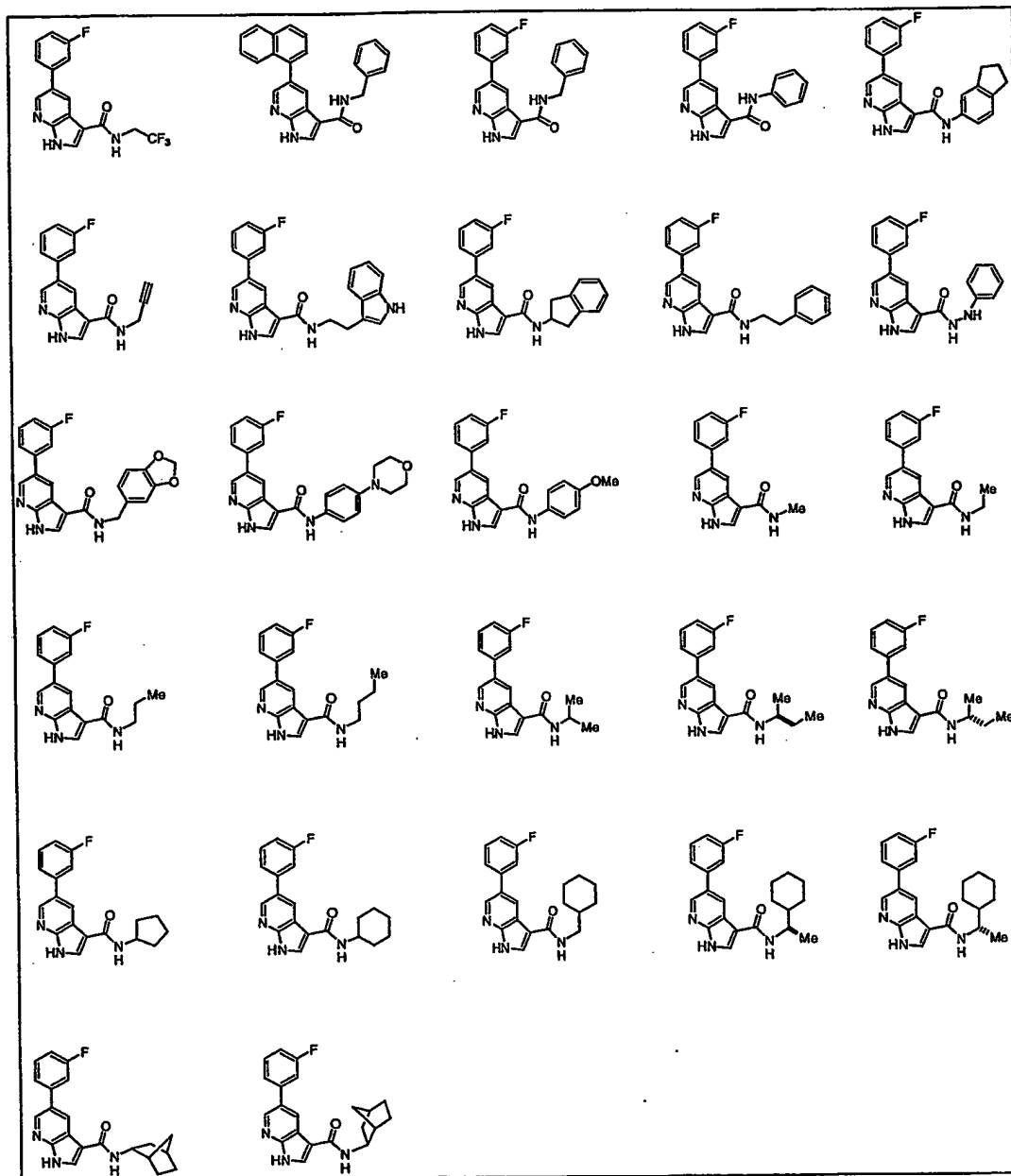
25 Y is absent or is NR^6 , O, CR^6R^6 , or C_{1-4} alkylene wherein each R^6 may be the same or different and is H, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} haloalkyl;

30 and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, including esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents or prodrugs thereof.

For the avoidance of doubt, when a group as defined above contains two or more radicals, e.g. the radical R^2 , as for example in the groups $SO_2NR^2R^2$ and NR^2COR^2 , the radicals R^2 may be the same or different.

- 5 Preferred R, R', X and Y groups for compounds of formula (Ia) are as defined for a compound of formula (I).

Representative compounds according to the first aspect of the invention are illustrated below.



The compounds of the invention may be provided as a salt, preferably as a pharmaceutically acceptable salt of compounds of formula (I). Examples of pharmaceutically acceptable salts of these compounds include those derived from organic acids such as acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid, methanesulphonic acid, benzenesulphonic acid and p-toluenesulphonic acid, mineral acids such as hydrochloric and sulphuric acid and the like, giving methanesulphonate, benzenesulphonate, p-toluenesulphonate, hydrochloride and sulphate, and the like, respectively or those derived from bases such as organic and inorganic bases. Examples of suitable inorganic bases for the formation of salts of compounds for this invention include the hydroxides, carbonates, and bicarbonates of ammonia, lithium, sodium, calcium, potassium, aluminium, iron, magnesium, zinc and the like. Salts can also be formed with suitable organic bases. Such bases suitable for the formation of pharmaceutically acceptable base addition salts with compounds of the present invention include organic bases which are nontoxic and strong enough to form salts. Such organic bases are already well known in the art and may include amino acids such as arginine and lysine, mono-, di-, or trihydroxyalkylamines such as mono-, di-, and triethanolamine, choline, mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and trimethylamine, guanidine; N-methylglucosamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; tris(hydroxymethyl) aminomethane; and the like.

25

Salts may be prepared in a conventional manner using methods well known in the art. Acid addition salts of said basic compounds may be prepared by dissolving the free base compounds according to the first or second aspects of the invention in aqueous or aqueous alcohol solution or other suitable solvents containing the required acid. Where a compound of the invention contains an acidic function, a base salt of said compound may be prepared by reacting said compound with a suitable base. The acid or base salt may separate directly or

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can be obtained by concentrating the solution e.g. by evaporation. The compounds of this invention may also exist in solvated or hydrated forms.

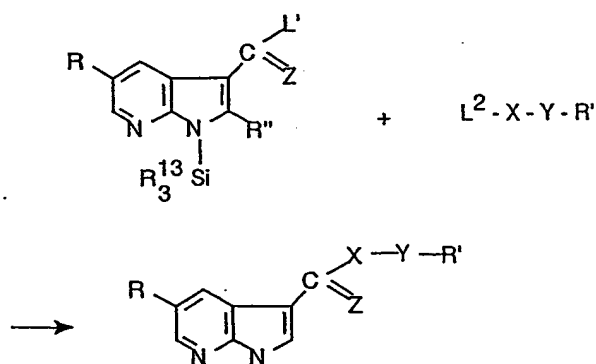
The invention also extends to a prodrug of the aforementioned compounds. A
 5 prodrug is any compound that may be converted under physiological conditions or by solvolysis to any of the compounds of the invention or to a pharmaceutically acceptable salt of the compounds of the invention. A prodrug may be inactive when administered to a subject but is converted *in vivo* to an active compound of the invention.

10

The compounds of the invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The first aspect of the invention covers all of these compounds.

15

The present invention also provides a process for the manufacture of any one or more of the compounds of the general formula (I) as defined above. According to the process, a compound of the general formula (II) in which R and R'' are as defined above and R¹³ stands for C₁₋₆ straight or branched alkyl, undergoes a condensation reaction with the compound of the general formula (III) to form
 20 the compound of the general formula (I) in which Z stands for oxygen.



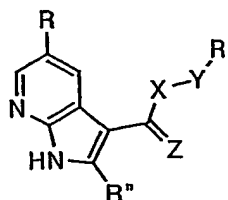
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In the formulae (II) and (III), L¹ and L² stand for radicals that together form a condensation product, e.g. H and OH or H and Cl. The condensation reaction occurs in a solution in a polar aprotic solvent such as e.g. dimethylformamide or dichloromethane under the influence of coupling agents such as, for instance WSCl, DCC, BOP, PyBrOP, etc., and in the presence of a tertiary amine.

(e.g. triethylamine) and 1-hydroxybenzotriazole (HOBT). Alternatively, the acid (II) may be first converted to an acid chloride by treatment with, for example, oxalyl chloride or thionyl chloride, and then without purification, reacted with, e.g. amines of formula (III).

5

The compound of the general formula (I) or (Ia)

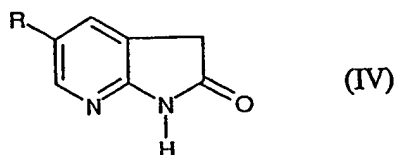


in which Z stands for O can be converted into the compounds of the general formula (I) in which Z stands for S by action of P_4S_{10} optionally in the presence of a base (e.g. pyridine), action of Lawesson's reagent in an aprotic solvent or other similar reagents. Compounds of general formula (I) or (Ia) in which $Z=O$ can be converted into the compounds of the general formula (I) in which Z stands for NR^7 by action of NH_2OH , NH_3 , primary amine/ $P(O)Cl_3$ system. They may also be prepared from (I) ($Z=S$) by the reaction with NH_2OH , NH_3 , hydrazine and its derivatives.

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In accordance with the present invention, the compound of the general formula (I) can be made from the compound of the general formula (IV).

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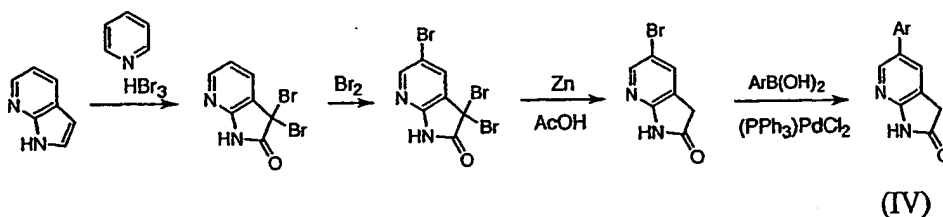
(IV)

The compound of the general formula (IV) can be made from 7-azaindole according to processes known in the art, see for example Glennon, K. C. *et al.* (WO00/56710) and Viaud, M.-C. *et al.* (EP0737685) and Cheung, M. *et al.* (WO99/21859).

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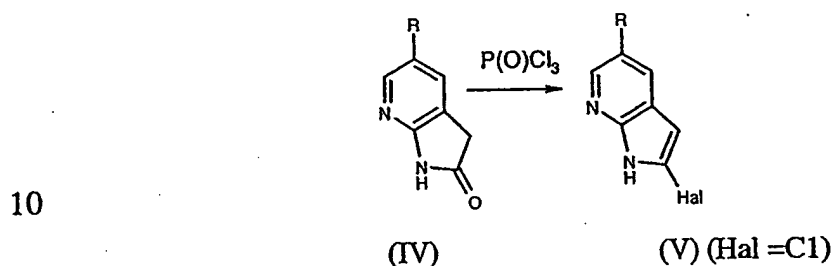
An example of a suitable scheme for the production of the compound of the general formula (IV) is:

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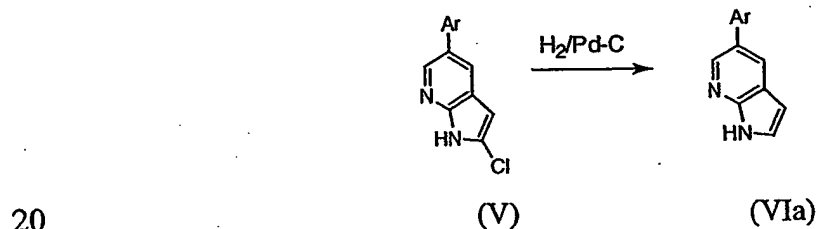


Compound (IV) can be halogenated in the 2 position to form a compound of the general formula (V) in which hal stands for a halogen, principally F or Cl.

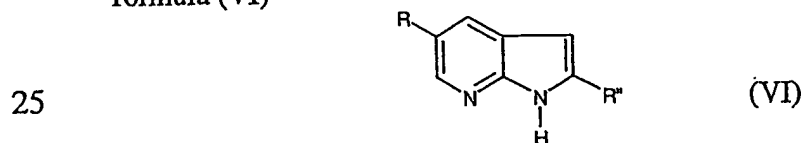
- 5 The halogen derivative (V) can be prepared from (IV), e.g. by the action of neat $P(O)Cl_3$ at elevated temperature (about $100^\circ C$), e.g.:



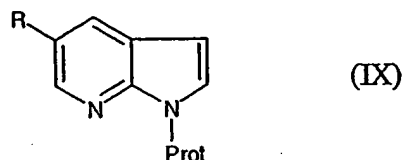
- (where R is an optionally substituted aryl group). Compound (V) can then be hydrogenated, e.g. with hydrogen in the presence of a suitable metal catalyst, such as e.g. palladium on activated carbon, and suitable amine such as e.g. triethylamine to form the compound of the general formula (VI) in which R'' stands for hydrogen. The reaction can be run using a solution of compound (V) in a single solvent (e.g. alcohol, such as methanol or ethanol) or a mixture of solvents including e.g. an alcohol, dichloromethane, chloroform, etc., e.g.



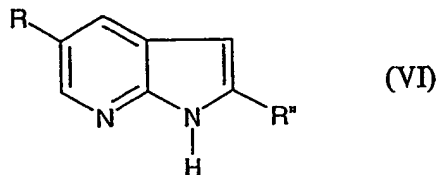
In order to make a compound of the general I in which R'' stands for a radical other than hydrogen, the R'' radical can be introduced into the compound of the formula (VI)



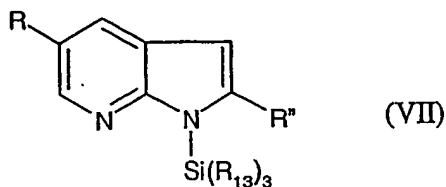
in which R'' stands for hydrogen by first of all protecting the nitrogen in the 1 position, e.g. with a phenylsulphonyl group which may be introduced following treatment with an alkyl lithium and reaction with the halide of the protecting group, e.g. phenylsulphonylhalide to form a compound of the general formula (IX) in which prot stands for a protecting group:



Group R'' (i.e. a radical other than hydrogen) can be introduced into compound (IX) using, for example, alkyl lithium followed by a halide of R'' to form a compound of the general formula (VI), in which R'' is a radical other than hydrogen:

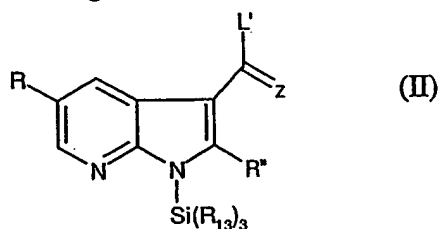


Compound (VI) (in which R'' is hydrogen or another radical as defined above) can be protected in the 1 position by trialkylsilanyl halide of the general formula $(R^{13})_3Si$ -halide in which R^{13} is as defined above for example by the action of a strong base, such as *n*-butyllithium on a solution of (VI) in a suitable solvent such as tetrahydrofuran, followed by trialkylsilanyl halide (either neat or as a solution in a suitable solvent) to form a compound of the general formula (VII):



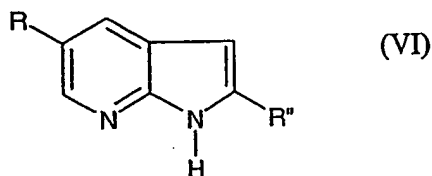
Compound (VII) can be halogenated in the 3 position, preferably by action of an equimolar amount of bromine (either neat or as a solution in a suitable solvent such as CCl_4 , CH_2Cl_2 , etc.) on a solution of compound (VII) in the same or similar solvent containing a slight excess of amine (e.g. pyridine), at or around room temperature to form a compound of general formula (VIII) (in which Hal stands for halogen, preferably bromine), which can be reacted with a alkali metal compound, e.g. alkyl lithium such as tertiary butyl lithium, followed by CO_2 to form the compound of the general formula (II)

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15 in which Z is O and L^1 is OH.

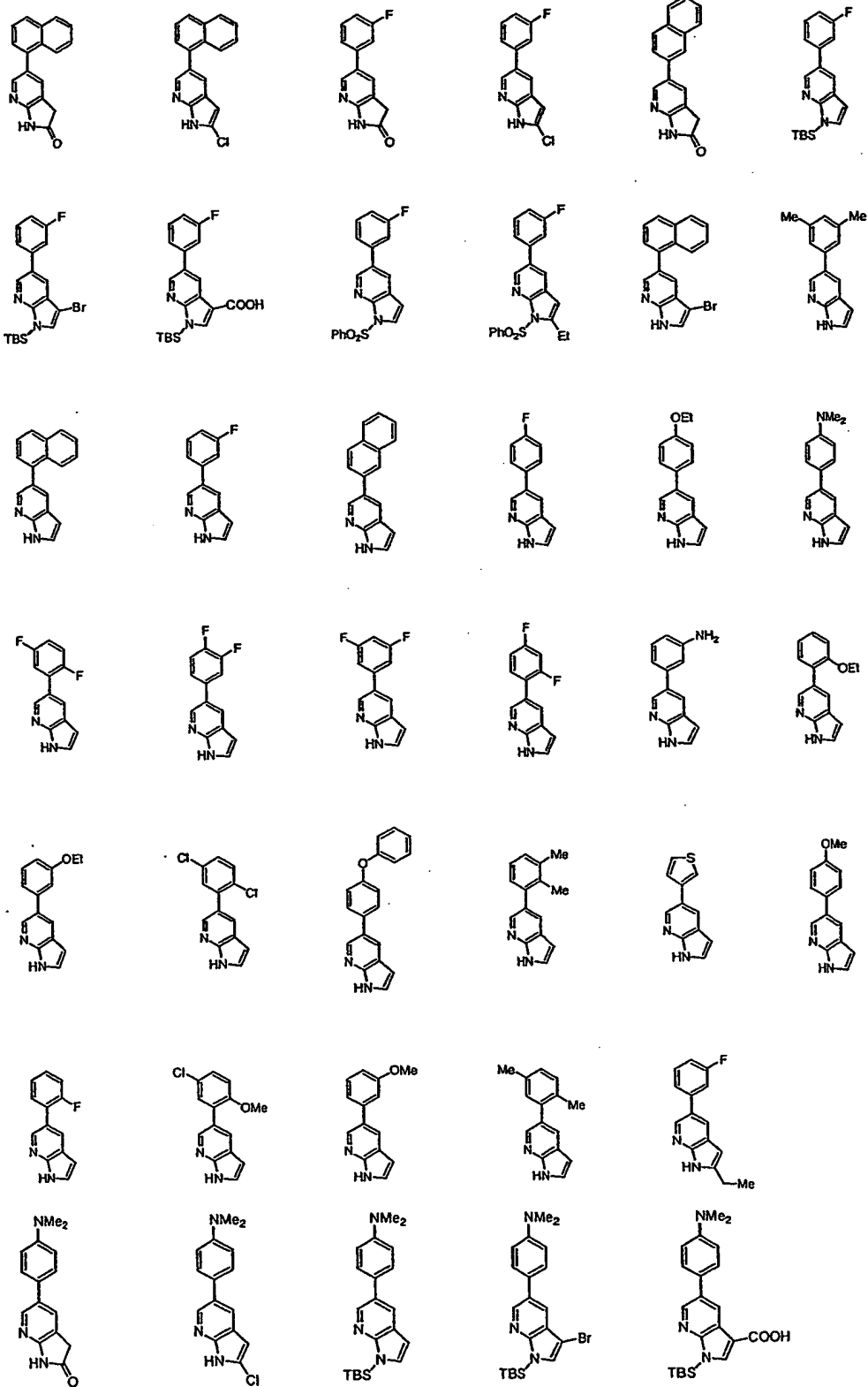
The use of the intermediates of the general formula (VI)

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wherein R' and R'' are as defined for the first aspect of the invention, in the manufacture of the compounds of the general formula (I) is novel and forms a third aspect of the present invention

Examples of intermediates of the third aspect are illustrated below:



An intermediate of the third aspect of the invention may be converted into another intermediate of the general formula (VI) by methods known in the art.

5 The present invention also encompasses a process for manufacturing a compound of the general formula (I), the process comprising providing a starting material, which is commercially available or can be produced by a method known in the art, converting the starting material to form an intermediate compound of the general formula (VI) using a process as described above or a process known in the art (and optionally converting the intermediate compound
10 so formed into another intermediate compound) and then converting the intermediate compound into a compound of the first aspect using a process as described above or a process known in the art (and optionally converting the compound of the general formula (I) so formed into another compound of the general formula).

15

The present invention also provides a composition comprising a compound of the general formula (I) or (Ia) as defined above in combination with a pharmaceutically acceptable carrier, diluent or excipient.

20 The composition may also comprise one or more additional active agent, such as an anti-inflammatory agent (for example a p38 inhibitor, glutamate receptor antagonist, or a calcium channel antagonist), a chemotherapeutic agent and/or an antiproliferative agent.

25 Suitable carriers and/or diluents are well known in the art and include pharmaceutical grade starch, mannitol, lactose, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, (or other sugar), magnesium carbonate, gelatin, oil, alcohol, detergents, emulsifiers or water (preferably sterile). The composition may be a mixed preparation of a composition or may
30 be a combined preparation for simultaneous, separate or sequential use (including administration).

The composition according to the invention for use in the aforementioned indications may be administered by any convenient method, for example by oral (including by inhalation), parenteral, mucosal (e.g. buccal, sublingual, nasal), rectal or transdermal administration and the compositions adapted accordingly.

5

For oral administration, the composition can be formulated as liquids or solids, for example solutions, syrups, suspensions or emulsions, tablets, capsules and lozenges.

10

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable aqueous or non-aqueous liquid carrier(s) for example water, ethanol, glycerine, polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

15

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and microcrystalline cellulose.

20

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, powders, granules or pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

25

Compositions for oral administration may be designed to protect the active ingredient against degradation as it passes through the alimentary tract, for example by an outer coating of the formulation on a tablet or capsule.

30

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous or non-aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or oral administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a pharmaceutically acceptable propellant. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal or vaginal administration are conveniently in the form of suppositories (containing a conventional suppository base such as cocoa butter), pessaries, vaginal tabs, foams or enemas.

Compositions suitable for transdermal administration include ointments, gels, patches and injections including powder injections.

Conveniently the composition is in unit dose form such as a tablet, capsule or ampoule.

In addition, the present invention provides a process for the manufacture of a composition according to the invention, as described above. The manufacture can be carried out by standard techniques well known in the art and involves combining a compound according to the first aspect of the invention and the pharmaceutically acceptable carrier or diluent. The composition may be in any form including a tablet, a liquid, a capsule, and a powder or in the form of a food product, e.g. a functional food. In the latter case the food product itself may act as the pharmaceutically acceptable carrier.

10

In addition, the present invention relates to a compound of the general formula (I) or (Ia) or a composition containing the compound, for use in therapy/medicine.

15

The compounds of the present invention are inhibitors of JNK, such as JNK1, JNK2, or JNK3. In particular, the compounds of the present invention are inhibitors of JNK3. Preferably, the compounds of the present invention inhibit JNK3 specifically.

20

One advantage of the compounds of the present invention is that they show a good stability to liver microsomes, at least when tested *in vitro* and hence are not rapidly metabolically removed from the body.

25

The compounds are therefore useful for conditions for which inhibition of JNK activity is beneficial. Thus, preferably, this aspect provides a compound of the general formula (I) or (Ia), or a composition of the present invention, as described above, for the prevention or treatment of a JNK-mediated disorder. The compounds of the general formula (I) or (Ia) may thus be used for the inhibition of JNK, more preferably for the inhibition of JNK3.

30

A "JNK-mediated disorder" is any disease or deleterious condition in which JNK plays a role. Examples include neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, proliferative

disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and any condition associated with prostaglandin endoperoxidase synthase-2. The compounds of the present invention may be used for any of these JNK-mediated disorders.

The compounds of the present invention are particularly useful for the prevention or treatment of a neurodegenerative disorder. In particular, the neurodegenerative disorder results from apoptosis and/or inflammation. Examples of neurodegenerative disorders are: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea; hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity including glutamate neurotoxicity; cerebral ischemia; dementia linked to meningitis and/or neurosis; cerebrovascular dementia; or dementia in an HIV-infected patient.

The neurodegenerative disorder may be a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy. Examples of peripheral neuropathy may be found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies, or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

30

The compounds of the invention can also be used to prevent or treat disorders resulting from inflammation. These include, for example, inflammatory bowel disorder, bronchitis, asthma, acute pancreatitis, chronic pancreatitis, allergies of

various types, and possibly Alzheimer's disease. Autoimmune diseases which may also be treated or prevented by the compounds of the present invention include rheumatoid arthritis, systemic lupus erythematosus, glomerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytic anaemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.

A compound of the present invention may be administered simultaneously, subsequently or sequentially with one or more other active agent, such as an anti-inflammatory agent e.g. p38 inhibitor, glutamate receptor antagonist, calcium channel antagonist, a chemotherapeutic agent or an antiproliferative agent. For example, for acute treatment, a p38 inhibitor may be administered to a patient prior to administering a compound of the present invention.

The compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 2000 mg, preferably between 30 mg and 1000 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or (Ia), or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Accordingly the present invention relates to a method of treating or preventing a JNK-mediated disorder in an individual, which method comprises administering to said individual a compound of the first aspect or a composition containing that compound. The active compound is preferably administered in a cumulative effective amount. The individual may be in need of the treatment or prevention. Any of the JNK-mediated disorders listed above in relation to the sixth aspect may be the subject of treatment or prevention according to the seventh aspect. One or more other active agent may be administered to the individual

simultaneously, subsequently or sequentially to administering the compound. The other active agent may be an anti-inflammatory agent such as a p38 inhibitor, glutamate receptor antagonist, calcium channel antagonist, a chemotherapeutic agent or an antiproliferative agent, but is preferably p38 inhibitor for acute treatment.

The present invention provides the use of a compound of the general formula (I) or (Ia) in the manufacture of a medicament for the prevention or treatment of a JNK-mediated disorder. The medicament may be used for treatment or prevention of any of the JNK-mediated disorders listed above in relation to the sixth aspect. Again, the compound of the present invention may be administered simultaneously, subsequently or sequentially with one or more other active agent, preferably a p38 inhibitor for acute treatment.

According to the present invention, there is also provided an assay for determining the activity of the compounds of the present invention, comprising providing a system for assaying the activity and assaying the activity of the compound. Preferably the assay is for the JNK inhibiting activity of the compound, more preferably it is for the JNK3-specific inhibiting activity of the compounds. The compounds of the invention may be assayed *in vitro*, *in vivo*, *in silico*, or in a primary cell culture or a cell line. *In vitro* assays include assays that determine inhibition of either the kinase activity or ATPase activity of activated JNK. Alternatively, *in vitro* assays may quantitate the ability of a compound to bind JNK and may be measured either by radiolabelling the compound prior to binding, then isolating the inhibitor/JNK complex and determining the amount of the radiolabel bound or by running a competition experiment where new inhibitors are incubated with JNK bound to known radioligands. An example of an assay which may be used is Scintillation Proximity Assay (SPA), preferably using radiolabelled ATP. Another example is ELISA. Any type or isoform of JNK may be used in these assays.

In a yet further aspect of the present invention, there is provided a method of inhibiting the activity or function of a JNK, particularly JNK3, which method comprises exposing a JNK to a compound or a composition of the first or fourth aspect of the present invention. The method may be performed in a research model, *in vitro*, *in silico*, or *in vivo* such as in an animal model. A suitable animal model may be a kainic acid model in rat or mice, traumatic brain injury model in rat, or MPTP in mice.

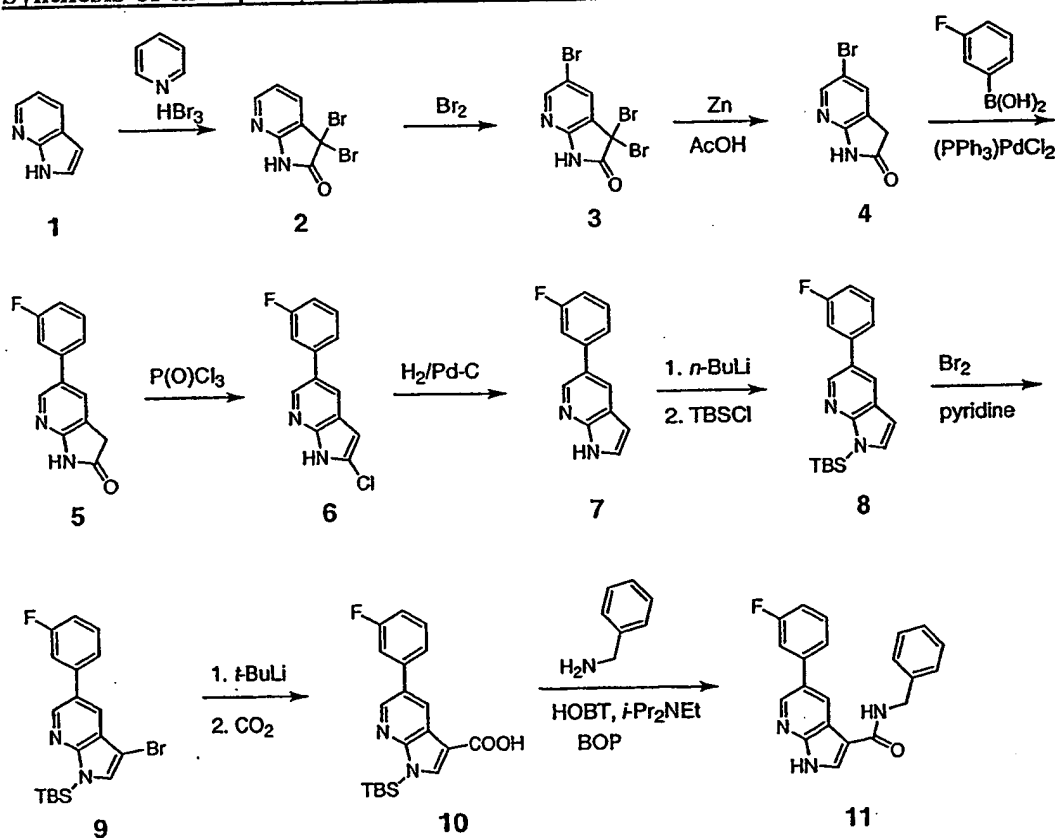
All features of each of the aspects apply to all other aspects *mutatis mutandis*.

10

Below, the present invention is illustrated using non-limiting examples.

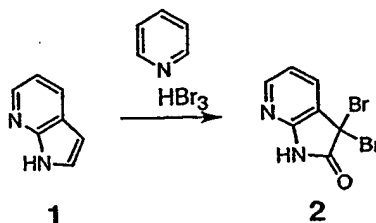
EXAMPLES

Synthesis of example 3,5-disubstituted 7-azaindole derivative 11

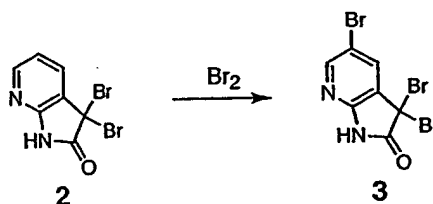


Scheme 1

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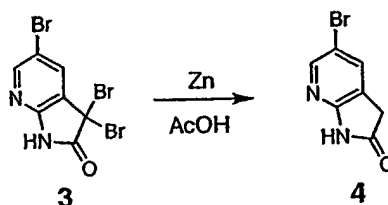
3,3-Dibromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (2)

Technical (90%) pyridinium tribromide (220.4 g, 0.62 mol) was added portionwise over a period of 30 min to a stirred suspension of 7-azaindole (1, 27.13 g, 0.23 mol) in *t*-BuOH (1.36 L). The mixture was stirred at r.t for 3 h, and more pyridinium tribromide (73.3 g, 0.21 mol) was added in one portion. After additional stirring at r.t. for 2 h, the solvent was evaporated under reduced pressure. The residue was separated between water:AcOEt=1:1 (4.2 L). The aqueous layer was extracted with AcOEt (2x800 mL). Combined organic solutions were washed with water (2x500 mL), brine, dried (MgSO₄) and concentrated to dryness in vacuum. The residue was triturated with CH₂Cl₂ (1500 mL) for 20 min. The solid was filtered off, washed with CH₂Cl₂ (250 mL) and dried in vacuum to afford 2 (49.85 g, 75%) as yellow powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.16 (dd, *J* = 7.4, 5.1 Hz, 1H), 7.98 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.19 (dd, *J* = 5.1, 1.5 Hz, 1H), 11.97 (bs, 1H).

3,3,5-Tribromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (3)

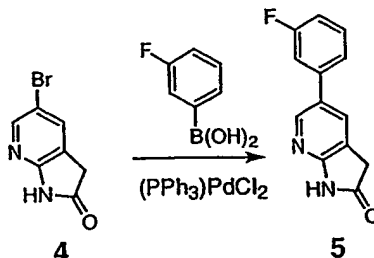
Bromine (13.4 mL, 0.262 mol) was added dropwise over a period of 30 min to a cooled (ice bath) and stirred suspension of 2 (37.86 g, 0.131 mol) in water:*t*-BuOH=1:1 (1500 mL). Cooling bath was removed and the mixture was stirred at r.t. overnight. Then the solution was cooled to 15 °C and saturated aqueous solution of NaHCO₃ (278 mL) was added. A yellow suspension, which was formed, was concentrated in vacuum (bath temperature < 32 °C) until about 1000 mL of condensate was collected. The solid was filtered off, washed with water (200 mL), and dried in vacuum to afford 3 (40.85 g, 85%) as tan powder.

5-Bromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (4)



Zinc dust (34.0 g, 0.52 mol) was added in small portion to a stirred suspension of 3 (40.85 g, 0.111 mol) in glacial acetic acid (1000 mL) at such a rate that the temperature was maintained between 20-25 °C (strongly exothermic reaction; external ice bath cooling). Addition took about 20 min. Cooling bath was removed and stirring was continued at r.t. for 2 h. The solid was filtered off, washed with toluene (50 mL) and triturated with CH₂Cl₂:MeOH=4:1 (2.5 L). The solution was decanted off and treated with 1.0 M aqueous Na₂CO₃ solution (170 mL). After stirring for 1 h the two layers were separated. The organic layer was washed again with 1.0 M aqueous Na₂CO₃ solution (50 mL). The combined aqueous layers were extracted with CH₂Cl₂:MeOH=4:1 (10x100 mL). Combined organic solutions were dried with MgSO₄ (200 g) and concentrated. The residual solid was dissolved in THF (2000 mL) and insoluble material was filtered off. The filtrate was concentrated to dryness in vacuum to afford 4 (16.93 g, 72%) as tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.57 (s, 2H), 7.75 (m, 1H), 8.14 (m, 1H), 11.13 (bs, 1H).

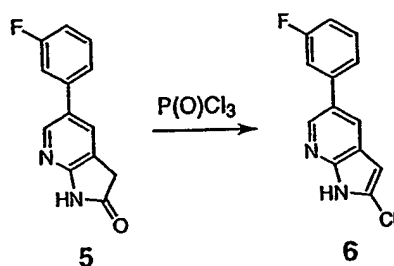
5-(3-Fluoro-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (5)



A mixture of 4 (16.63 g, 78.5 mmol), 3-fluorophenylboronic acid (16.47 g, 117.7 mmol), Pd(PPh₃)₂Cl₂ (2.73 g, 6.60 mmol), LiCl (9.95 g, 0.23 mol), 1.0 M aqueous Na₂CO₃ solution (196 mL, 0.196 mol) in EtOH (470 mL) – toluene (470 mL) was refluxed overnight. More Pd(PPh₃)₂Cl₂ (1.30 g, 3.14 mmol) was added and reflux was continued for 24 h. The mixture was cooled, and the

organic layer was separated and washed with brine (100 mL). The washings were combined with the aqueous layer and extracted with AcOEt (4x400 mL). Combined extracts were washed with brine, added to the organic layer and dried with MgSO₄. The solution was concentrated to dryness in vacuum to give 26.98 g of brown semisolid, which was triturated with ether:hexane=1:1 (2x500 mL). The residue was dried in vacuum to afford 5 (16.85 g, 94%) as tan solid, which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 2H), 7.08 (dddd, *J* = 8.4, 8.2, 2.4, 0.9 Hz, 1H), 7.22 (ddd, *J* = 10.0, 2.4, 1.7 Hz, 1H), 7.30 (ddd, *J* = 8.1, 1.7, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.2, 8.1, 6.0 Hz, 1H), 7.69 (s, 1H), 8.36 (d, *J* = 2.1 Hz, 1H), 8.98 (bs, 1H).

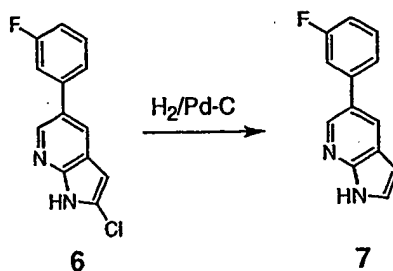
2-Chloro-5-(3-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine (6)



A suspension of 5 (16.52 g, 72.4 mmol) in neat P(O)Cl₃ (21.5 mL, 0.231 mol) was stirred at 100-105 °C for 4 h. The mixture was then cooled to r.t., diluted with *p*-xylene (100 mL) and concentrated to dryness in vacuum. The residue was separated between saturated aqueous NaHCO₃ – AcOEt. 10% aqueous solution of Na₂CO₃ was added to basify the aqueous layer to pH 9. Organic phase was separated and the aqueous layer was extracted with AcOEt (8x300 mL). Combined organic solutions were dried MgSO₄, concentrated, and the residue was purified by silicagel chromatography (SGC) using CH₂Cl₂:AcOEt as eluent in gradient to afford recovered starting material 5 (0.76 g, 5%). The desired product was then crystallized from acetone to afford 6 (10.06 g, 56%), thin tan needles. ¹H NMR (400 MHz, CDCl₃) δ 6.47 (s, 1H), 7.08 (tdd, *J* = 8.1, 2.3, 1.5 Hz, 1H), 7.33 (ddd, *J* = 9.9, 2.3, 1.6 Hz, 1H), 7.38-7.48 (m, 2H), 8.03 (d, *J* = 2.1 Hz, 1H), 8.53 (d, *J* = 2.1 Hz, 1H), 11.46 (bs, 1H).

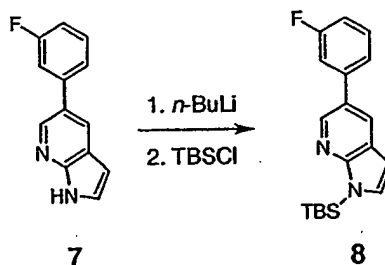
5-(3-Fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine (7)

35



A mixture of chloride 6 (5.23 g, 21.3 mmol), 10% Pd/C (2.7 g), Et₃N (3.6 mL, 25.8 mmol) in THF:MeOH=5:1 (180 mL) was stirred under H₂ overnight. More 10% Pd/C (1.3 g) was added and stirring was continued for 3 h. Catalyst was removed by filtration and the solution was concentrated to dryness in vacuum. The residue was purified by SGC with CH₂Cl₂:AcOEt as eluent in gradient (up to 20% AcOEt) to afford 7 (5.23 g, 88%), greenish powder. ¹H NMR (400 MHz, CDCl₃) δ 6.59 (dd, *J* = 3.5, 2.0 Hz, 1H), 7.04-7.10 (m, 1H), 7.33-7.37 (m, 1H), 7.40-7.48 (m, 3H), 8.14 (d, *J* = 2.1 Hz, 1H), 8.57 (d, *J* = 2.1 Hz, 1H), 9.91 (bs, 1H).

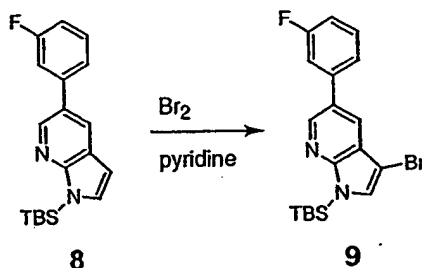
1-(tert-Butyl-dimethyl-silanyl)-5-(3-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine (8)



2.5 M solution of *n*-BuLi in hexane (13.7 mL, 34.3 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of azaindole 7 (6.04 g, 28.5 mmol) in THF (30 mL). After the mixture was stirred for 10 min at -78 °C, DMAP (66 mg, 0.54 mmol) was added, followed by a solution of TBSCl (5.14 g, 34.1 mmol) in THF (2.5 mL). The mixture was stirred at -78 °C for 1 h. Cooling bath was removed, the mixture was stirred at r.t. for 3 days, and separated between AcOEt:saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with AcOEt (3x). Combined organic solutions were dried (MgSO₄), concentrated, and separated by means of SGC with hexane:benzene as eluent in gradient (up to 15 % benzene) to afford 8 (7.50 g, 81%) as white solid. ¹H NMR

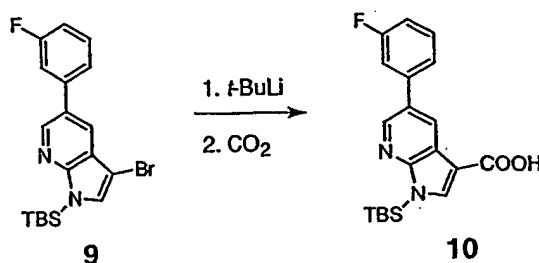
(400 MHz, CDCl_3) δ 0.67 (s, 6H), 0.96 (s, 9H), 6.59 (d, $J = 3.5$ Hz, 1H), 6.99-7.07 (m, 1H), 7.29 (d, $J = 3.5$ Hz, 1H), 7.33 (ddd, $J = 10.9, 3.0, 1.7$ Hz, 1H), 7.38-7.44 (m, 2H), 8.04 (d, $J = 2.3$ Hz, 1H), 8.51 (d, $J = 2.3$ Hz, 1H).

5 **3-Bromo-1-(tert-butyl-dimethyl-silanyl)-5-(3-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine (9)**



A solution of Br_2 (1.12 mL, 21.8 mmol) in CCl_4 was added dropwise to a stirred and cooled (0°C) solution of 8 (7.10 g, 21.8 mmol) and pyridine (2.1 mL, 26.2 mmol) in dry CHCl_3 (330 mL). Progress of the reaction was followed by TLC. When the reaction was completed, aqueous $\text{NaHCO}_3 - \text{Na}_2\text{S}_2\text{O}_3$ solution was added. The organic solution was separated and the aqueous layer was extracted with CH_2Cl_2 (3x100 mL). Combined organic solutions were dried (MgSO_4), concentrated and purified by SGC with hexane:benzene as eluent in gradient (up to 14% benzene) to afford 9 (8.47 g, 91%) as tan solid. ^1H NMR (400 MHz, CDCl_3) δ 0.65 (s, 6H), 0.97 (s, 9H), 7.02-7.10 (m, 1H), 7.29 (s, 1H), 7.33-7.38 (m, 1H), 7.40-7.47 (m, 2H), 7.97 (d, $J = 2.2$ Hz, 1H), 8.51 (d, $J = 2.2$ Hz, 1H).

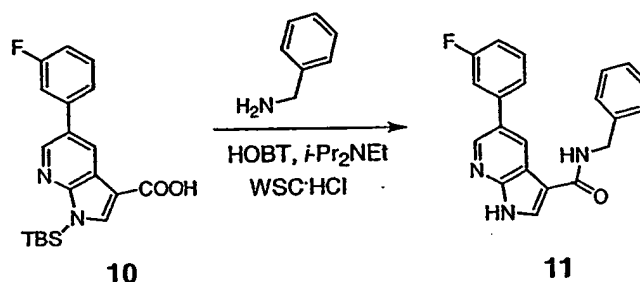
20 **1-(tert-Butyl-dimethyl-silanyl)-5-(3-fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid (10)**



1.7 M solution of $t\text{-BuLi}$ in pentane (24.8 mL, 42.2 mmol) was added dropwise over a period of 25 min to a stirred and cooled (-78°C) solution of 9 (8.20 g, 20.3 mmol) in THF (93 mL) at such a rate that the temperature did not exceed –

65 °C. After the addition, the mixture was stirred for 1 h at -78 °C. Dry gaseous CO₂ was introduced to the flask over a period of 10 min (exothermic reaction, external dry ice bath). When the exothermic reaction subsided, cooling bath was removed, and the mixture was allowed to reach 0 °C. The mixture was then separated between brine-AcOEt. The aqueous layer was extracted with AcOEt (2x). Combined organic solutions were dried (MgSO₄), concentrated and purified by SGC with CH₂Cl₂:AcOEt as eluent in gradient (up to 12% AcOEt) to afford **10** (5.74 g, 76%) as tan solid. ¹H NMR (400 MHz, CDCl₃) δ 0.71 (s, 6H), 0.99 (s, 9H), 7.05-7.12 (m, 1H), 7.37-7.42 (m, 1H), 7.43-7.50 (m, 2H), 8.11 (s, 1H), 8.58 (d, *J* = 2.3 Hz, 1H), 8.61 (d, *J* = 2.3 Hz, 1H).

5-(3-Fluoro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid benzylamide (11)

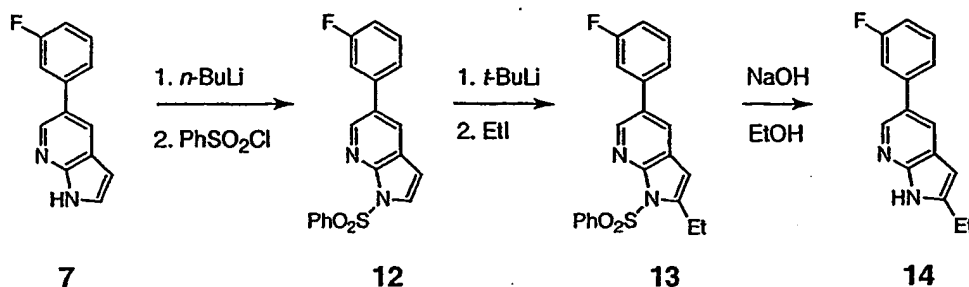


To a solution of benzylamine (4.4 μL, 40.3 μmol) in dry CH₂Cl₂ (0.5 mL) was added carboxylic acid **10** (15 mg, 40.5 μmol), WSCl (9.32 mg, 44.86 μmol), HOBT (5.5 mg, 40.5 μmol) and *i*-Pr₂NEt (7.1 μL, 40.8 μmol) and the reaction mixture left to stir at r.t. overnight. Separation by LCMS (CombiPrep ODS-AM column) using water – acetonitrile as eluent (in gradient) afforded amide **11** (2.33 mg, 17 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.70 (d, *J* = 5.5 Hz, 2H), 6.18 (t, *J* = 5.5 Hz, 1H), 7.29-7.44 (m, 8H), 7.80 (s, 1H), 8.57 (d, *J* = 1.8 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H).

An example of the synthesis of the intermediate VI in which R'' is not hydrogen will now be described:

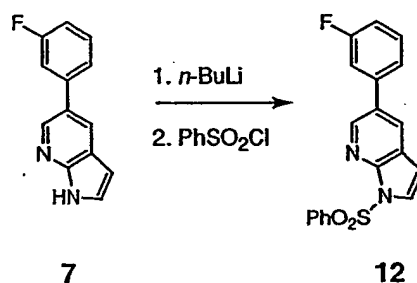
Synthesis of example 2,5-disubstituted 7-azaindole derivative 14

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Scheme 2

1-Benzenesulfonyl-5-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine (12)

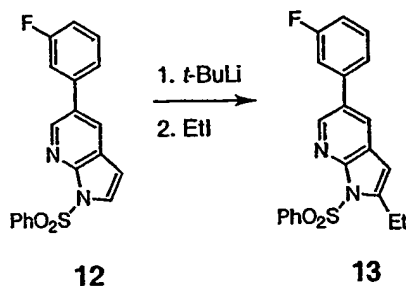


- 5 2.5 M solution of *n*-BuLi in hexane (2.47 mL, 6.18 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of azaindole 7 (1.088 g, 5.13 mmol) in THF (5.5 mL). After the mixture was stirred for 20 min at -78 °C, neat PhSO₂Cl (0.785 mL, 6.2 mmol) was added dropwise. The mixture turned brown. Stirring at -78 °C was continued for 0.5 h. Cooling bath was removed, the mixture was
- 10 stirred at r.t. overnight, and separated between AcOEt:saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with AcOEt (2x5 mL). Combined organic solutions were washed with brine, dried (MgSO₄), concentrated, and separated by means of SGC with hexane:AcOEt as eluent in gradient to afford 12 (1.6705 g, 92%) as white solid. ¹H NMR (400 MHz,
- 15 CDCl₃) δ 6.66 (d, *J* = 4.0 Hz, 1H), 7.08 (dddd, *J* = 8.4, 8.0, 2.5, 1.1 Hz, 1H), 7.25 (ddd, *J* = 9.9, 2.5, 1.7 Hz, 1H), 7.33 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.43 (ddd, *J* = 8.0, 7.8, 6.0 Hz, 1H), 7.47-7.53 (m, 2H), 7.57-7.62 (m, 1H), 7.78 (d, *J* = 4.0 Hz, 1H), 7.99 (d, *J* = 2.2 Hz, 1H), 8.21-8.26 (m, 2H), 8.63 (d, *J* = 2.2 Hz, 1H).

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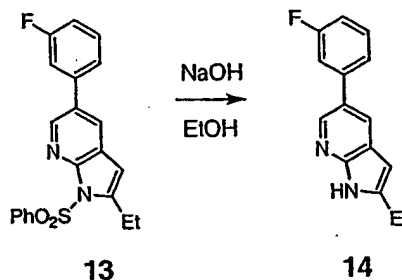
1-Benzenesulfonyl-2-ethyl-5-(3-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine (13)

39



1.7 M solution of *t*-BuLi in pentane (0.71 mL, 1.20 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of 12 (352.0 mg, 1.00 mmol) in THF (2.0 mL). The mixture turned red-brown. After the addition, the mixture was stirred for 30 min at -78 °C. Neat EtI (150 µL, 1.88 mol) was added in one portion, and the mixture was allowed to reach 0 °C over a period of 1 h 15 min. The reaction was quenched by the addition of saturated aqueous NaHCO₃ solution. The mixture was then extracted with AcOEt (3x3 mL). Combined organic solutions were washed with brine, dried (MgSO₄), concentrated and purified by SGC with hexane:AcOEt as eluent in gradient to afford 13 (138.5 mg, 36%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.42 (t, *J* = 7.3 Hz, 3H), 3.21 (qd, *J* = 7.3, 1.2 Hz, 2H), 6.39 (t, *J* = 1.2 Hz, 1H), 7.07 (dddd, *J* = 8.4, 8.0, 2.5, 1.0 Hz, 1H), 7.25 (ddd, *J* = 9.9, 2.5, 1.7 Hz, 1H), 7.34 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.42 (ddd, *J* = 8.0, 7.7, 5.9 Hz, 1H), 7.46-7.51 (m, 2H), 7.54-7.60 (m, 1H), 7.86 (d, *J* = 2.2 Hz, 1H), 8.15-8.19 (m, 2H), 8.57 (d, *J* = 2.2 Hz, 1H).

2-Ethyl-5-(3-fluorophenyl)-1H-pyrrolo[Z₁3-b]pyridine(14).



A mixture of 13 (50.0 mg; 0.132 mmol) and 10% aqueous solution of NaOH (1.5 mL) in abs EtOH (3.0 mL) was refluxed for 40 min, cooled and diluted with water (10 mL). White precipitate which appeared was filtered off, washed with water (10 mL) and dried in vacuum to afford 14 (27.95 mg, 88%) as white solid.

^1H NMR (400 MHz, CDCl_3) δ 1.42 (t, $J = 7.6$ Hz, 3H), 2.89 (qd, $J = 7.6, 0.8$ Hz, 2H), 6.27 (dt, $J = 2.1, 0.8$ Hz, 1H), 7.02-7.09 (m, 1H), 7.30-7.36 (m, 1H), 7.38-7.46 (m, 2H), 7.99 (dd, $J = 2.1, 0.6$ Hz, 1H), 8.43 (d, $J = 2.1$ Hz, 1H), 9.70 (bs, 1H).

5

Examples of inhibitory potency against JNK3 kinase

JNK1, JNK2, JNK3 - SPA assay

10 A typical assay for testing the activity of compounds to inhibit JNK1, JNK2 and JNK3 enzymes is as follows:

- 15 1. Compound is dissolved in DMSO to a convenient concentration and this is diluted in 10% DMSO to a five times concentrate of the desired starting concentration (frequently 1:100).
- 20 2. 10 μl of 500 mM EDTA is added to alternative wells of the Opti-plate row, which will receive kinase reaction plus DMSO. This creates the negative control.
- 25 3. For the JNK2 and JNK3 assay, compounds are prepared in six 2-fold dilutions with water and each concentration is tested in duplicate. For the JNK1 assay compounds are prepared in four 5-fold dilutions with water which are tested in triplicate. Controls are treated identically.
- 30 4. 20 μl per well of each compound concentration is transferred to an Opti-plate, in duplicate.
5. 30 μl (JNK2/3 SPA) or 50 μl (JNK1 SPA) of substrate solution (25 mM HEPES pH 7.5, 10mM magnesium acetate with 3.33 μM ATP (JNK2/3) or 2 μM ATP (JNK1), approximately 7.5 kBq [γ -33P] ATP, GST-c-Jun, in water) is added to each well.

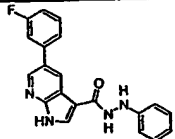
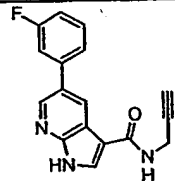
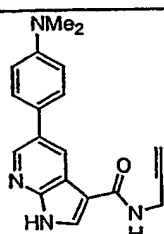
6. 50 μ l (JNK2/3 SPA) or 30 μ l (JNK1 SPA) of kinase solution (JNK in 25 mM HEPES pH 7.5, 10mM Mg Acetate) is added to each well.

| Kinase | Kinase per well (μ g) | GST-c-Jun per well (μ g) |
|--------|----------------------------|-------------------------------|
| JNK1 | 0.25 | 1 |
| JNK2 | 0.2 | 1.2 |
| JNK3 | 0.16 | 1.2 |

- 5 7. The plate is incubated for 30 minutes at room temperature.
8. 100 μ l of bead/stop solution is added to each well (5 mg/ml glutathione-PVT-SPA beads, 40 mM ATP in PBS).
- 10 9. Plates are sealed and incubated for 30 minutes at room temperature, centrifuged for 10 minutes at 2500g and counted.
10. The IC50 values are calculated as the concentration of the compound being tested at which the phosphorylation of c-Jun is decreased to 50% of the control value. Example IC50 values for the compounds of this invention are given in Table 1.
- 15

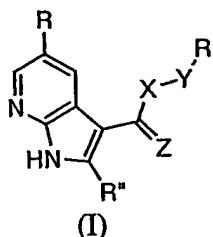
Examples of inhibitory potency against JNK3 kinase

Table 1. IC₅₀ values for selected compounds against JNK3 kinase

| Compound | JNK3 IC ₅₀ (μM) |
|---|-------------------------------|
|  | 0.78 |
|  | 0.85 |
|  | 0.52 |

Claims

1. A compound of formula (I) as defined below:



wherein:

10 R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

15 each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R²,
20 wherein each R² may be the same or different and is as defined below and wherein:

the C₁₋₁₂ alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O)₂- wherein each R² may be the same or different and is
25 as defined below;

the C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R²;
30 wherein each R² may be the same or different and is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C₁₋₁₂ alkyl,

each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, =NNHR², NNR²R², =N-OR²,
 5 =NNHCOR², =NNHCO₂R², =NNSO₂R², or =NR², wherein each R² may be the same or different and is as defined below; and

each substitutable nitrogen atom in R is optionally substituted by R³, COR², SO₂R² or CO₂R², wherein each R² and R³ may be the same or different and is as defined below;

10 R² is hydrogen, C₁₋₁₂ alkyl or aryl, optionally substituted by one or more of C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, OR⁴, SR⁴, NO₂, CN, NR⁴R⁴, NR⁴COR⁴, NR⁴CONR⁴R⁴, NR⁴COR⁴, NR⁴CO₂R⁴, CO₂R⁴, COR⁴, CONR⁴₂, S(O)₂R⁴, SONH₂, S(O)R⁴, SO₂ NR⁴R⁴, NR⁴S(O)₂R⁴, wherein the C₁₋₁₂ alkyl group optionally incorporates one or two insertions
 15 selected from the group consisting of -O-, -N(R⁴)-, -S(O)- and -S(O₂)-, wherein each R⁴ may be the same or different and is as defined below;

R³ is C₁₋₁₂ alkyl or aryl, optionally substituted by one or more of C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, OR⁴, SR⁴, NO₂, CN, NR⁴R⁴, NR⁴COR⁴, NR⁴CONR⁴R⁴, NR⁴COR⁴, NR⁴CO₂R⁴, CO₂R⁴, COR⁴, CONR⁴₂, S(O)₂R⁴,
 20 SONH₂, S(O)R⁴, SO₂ NR⁴R⁴, NR⁴S(O)₂R⁴, wherein the C₁₋₁₂ alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R⁴)-, -S(O)- and -S(O₂)-, wherein each R⁴ may be the same or different and is as defined below;

R⁴ is hydrogen, C₁₋₄ alkyl, or C₁₋₄ haloalkyl;

25

R' is C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, carbocyclyl or heterocyclyl, each of which is optionally substituted, wherein:

the optionally substituted carbocyclyl or heterocyclyl group is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered rings containing zero to
 30 three heteroatoms,

each substitutable carbon atom in R', including the optional fused ring, is optionally and independently substituted by one or more

of C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, heteroaryl halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂ NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined above and wherein:

the C₁₋₁₂ alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O)₂-, wherein each R² may be the same or different and is as defined above;

the C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one or more of halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined above; and

the C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one or more C₁₋₁₂ alkyl groups;

each saturated carbon in R', including the optional fused ring, is further optionally and independently substituted by =O, =S, NNR²R², =N-OR², =NNHCOR², =NNHCO₂R², =NNSO₂R², or =NR², wherein each R² may be the same or different and is as defined above; and

each substitutable nitrogen atom in R' is optionally substituted by R³, COR², SO₂R² or CO₂R² wherein each R² and R³ may be the same or different and is as defined above;

R'' is hydrogen, C₁₋₁₂ alkyl, carbocyclyl or heterocyclyl, each of which is optionally substituted, wherein:

the said carbocyclyl or heterocyclyl is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms, each substitutable carbon atom in R'', including the optional fused ring, is optionally and independently substituted by one or more of C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, heteroaryl, halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂ NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined below and wherein:

the C₁₋₁₂ alkyl group optionally incorporate one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O)₂-;

the C₁₋₁₂ alkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, and heteroaryl groups are optionally substituted by one or more of halogen, haloalkyl, unsaturated or partly saturated cycloalkyl, aryl, or heteroaryl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂ NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined above; and

the C₃₋₁₂ cycloalkyl, C₃₋₁₂ heterocycloalkyl, aryl, and heteroaryl groups, are optionally substituted by one or more C₁₋₁₂ alkyl

each saturated carbon in R'', including the optional fused ring, is further optionally and independently substituted by =O, =S, NNR²R², =N-OR², =NNHCOR², =NNHCO₂R², =NNSO₂R², or =NR², wherein each R² may be the same or different and is as defined above; and

each substitutable nitrogen atom in R'' is optionally substituted by R³, COR², SO₂ R² or CO₂ R², wherein each R² and R³ may be the same or different and is as defined above;

X is NR^5 ; O, S or C_{1-4} alkylene that is optionally substituted by one or more of halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN, NR^2R^2 , NR^2COR^2 , $\text{NR}^2\text{CONR}^2\text{R}^2$, NR^2COR^2 , $\text{NR}^2\text{CO}_2\text{R}^2$, CO_2R^2 , COR^2 , CONR^2R^2 , $\text{S(O)}_2\text{R}^2$, SONH_2 , S(O)R^2 , $\text{SO}_2\text{NR}^2\text{R}^2$, $\text{NR}^2\text{S(O)}_2\text{R}^2$, wherein each R^2 may be the same or different and is as defined above and R^5 is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkyl; and

Y is absent or is NR^6 , O, CR^6R^6 , or C_{1-4} alkylene wherein each R^6 may be the same or different and is H, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} haloalkyl; and

Z is O, S or NR^7 wherein each R^7 may be the same or different and is hydrogen, C_{1-4} alkyl optionally substituted with one or more of halide, OR^8 , NR^8R^8 or aryl, where each R^8 may be the same or different and stand for H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkoxy;

and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, including esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents or prodrugs thereof.

2. A compound as claimed in claim 1, having the formula (Ia);



wherein

R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R², wherein each R² may be the same or different and is as defined below and wherein:

the C₁₋₁₂ alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R²)-, -S(O)- and -S(O₂)- wherein each R² may be the same or different and is as defined below;

the C₁₋₁₂ alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR², SR², NO₂, CN, NR²R², NR²COR², NR²CONR²R², NR²COR², NR²CO₂R², CO₂R², COR², CONR²R², S(O)₂R², SONH₂, S(O)R², SO₂NR²R², NR²S(O)₂R²; wherein each R² may be the same or different and is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C₁₋₁₂ alkyl,

each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, =NNHR², NNR²R², =N-OR², =NNHCOR², =NNHCO₂R², =NNSO₂R², or =NR², wherein each R² may be the same or different and is as defined below; and

each substitutable nitrogen atom in R is optionally substituted by R³, COR², SO₂R² or CO₂R², wherein each R² and R³ may be the same or different and is as defined below;

R² is hydrogen, C₁₋₁₂ alkyl or aryl, optionally substituted by one or more of C₁₋₄ alkyl, halogen, C₁₋₄ haloalkyl, OR⁴, SR⁴, NO₂, CN, NR⁴R⁴, NR⁴COR⁴, NR⁴CONR⁴R⁴, NR⁴COR⁴, NR⁴CO₂R⁴, CO₂R⁴, COR⁴, CONR⁴, S(O)₂R⁴, SONH₂, S(O)R⁴, SO₂NR⁴R⁴, NR⁴S(O)₂R⁴, wherein the C₁₋₁₂ alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R⁴)-, -S(O)- and -S(O₂)-, wherein each R⁴ may be the same or different and is as defined below;

5 R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4 , SR^4 , NO_2 , CN , NR^4R^4 , NR^4COR^4 , $NR^4CONR^4R^4$, NR^4COR^4 , $NR^4CO_2R^4$, CO_2R^4 , COR^4 , $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, $SO_2NR^4R^4$, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of $-O-$, $-N(R^4)-$, $-S(O)-$ and $-S(O_2)-$, wherein each R^4 may be the same or different and is as defined below;

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

10 R' is C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, carbocyclyl or heterocyclyl, each of which is optionally substituted, wherein:

the optionally substituted carbocyclyl or heterocyclyl group is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered rings containing zero to three heteroatoms,

15 each substitutable carbon atom in R' , including the optional fused ring, is optionally and independently substituted by one or more of C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, aryl, heteroaryl halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN , NR^2R^2 , NR^2COR^2 , $NR^2CONR^2R^2$, NR^2COR^2 , $NR^2CO_2R^2$, CO_2R^2 , COR^2 , $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$, wherein each R^2 may be the same or different and is as defined above and wherein:

25 the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of $-O-$, $-C(O)-$, $-N(R^2)-$, $-S(O)-$ and $-S(O_2)-$, wherein each R^2 may be the same or different and is as defined above;

30 the C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one or more of halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN , NR^2R^2 , NR^2COR^2 , $NR^2CONR^2R^2$, NR^2COR^2 , $NR^2CO_2R^2$, CO_2R^2 , COR^2 , $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$,

$\text{SO}_2\text{NR}^2\text{R}^2$, $\text{NR}^2\text{S}(\text{O})_2\text{R}^2$, wherein each R^2 may be the same or different and is as defined above; and

the C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, aryl, or heteroaryl groups are optionally substituted by one or more C_{1-12} alkyl groups;

each saturated carbon in R' , including the optional fused ring, is further optionally and independently substituted by $=\text{O}$, $=\text{S}$, NNR^2R^2 , $=\text{N}-\text{OR}^2$, $=\text{NNHCO}\text{R}^2$, $=\text{NNHCO}_2\text{R}^2$, $=\text{NNSO}_2\text{R}^2$, or $=\text{NR}^2$, wherein each R^2 may be the same or different and is as defined above; and

each substitutable nitrogen atom in R' is optionally substituted by R^3 , COR^2 , SO_2R^2 or CO_2R^2 wherein each R^2 and R^3 may be the same or different and is as defined above;

15 X is NR^5 ; O, S or C_{1-4} alkylene that is optionally substituted by one or more of halogen, haloalkyl, OR^2 , SR^2 , NO_2 , CN, NR^2R^2 , NR^2COR^2 , $\text{NR}^2\text{CONR}^2\text{R}^2$, NR^2COR^2 , $\text{NR}^2\text{CO}_2\text{R}^2$, CO_2R^2 , COR^2 , CONR^2R^2 , $\text{S}(\text{O})_2\text{R}^2$, SONH_2 , $\text{S}(\text{O})\text{R}^2$, $\text{SO}_2\text{NR}^2\text{R}^2$, $\text{NR}^2\text{S}(\text{O})_2\text{R}^2$, wherein each R^2 may be the same or different and is as defined above and R^5 is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl or C_{1-4} haloalkyl; and

20 Y is absent or is NR^6 , O, CR^6R^6 , or C_{1-4} alkylene wherein each R^6 may be the same or different and is H, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} haloalkyl.

25

3. A compound as claimed in claim 1 or claim 2, wherein R is an aryl or heteroaryl radical, optionally substituted with one or more of alkyl, haloalkyl, halogen, OR^9 , SR^8 , SOR^9 , $\text{N}(\text{R}^9)_2$, wherein each R^9 may be the same or different and stand for hydrogen, C_{1-4} alkyl or haloalkyl.

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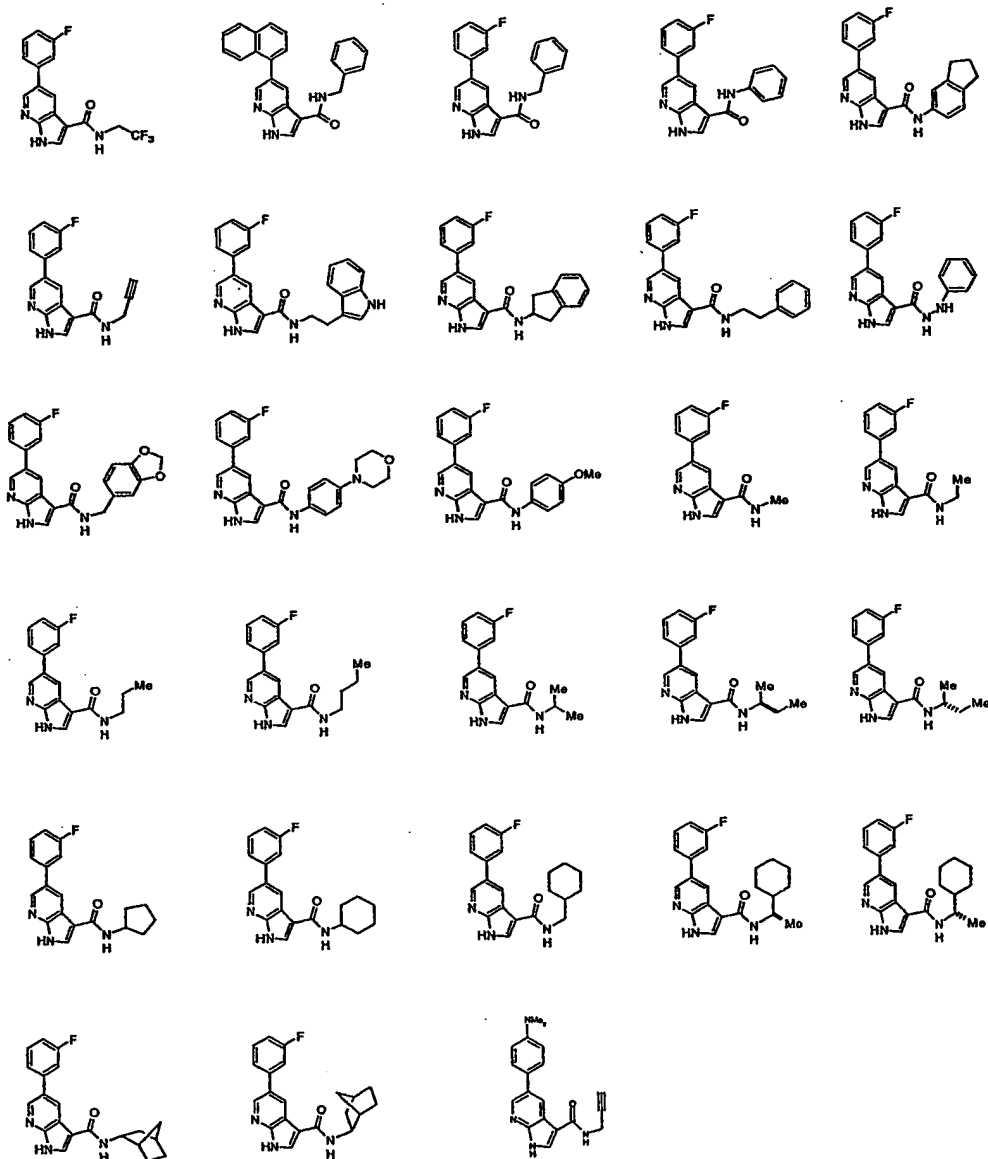
4. A compound as claimed in any one of claims 1 to 3 wherein R is an optionally substituted aryl, preferably phenyl or naphthyl.

5. A compound as claimed in claim 4, wherein R is phenyl substituted in the 3-(meta) position.
6. A compound as claimed in claim 4 or claim 5, wherein R is substituted aryl and the substituent is F, Cl or Br, preferably F; or haloalkyl, preferably CF₃, or alkyl, preferably methyl, ethyl or propyl.
7. A compound as claimed in any one of claims 1 to 6, wherein R' is C₁₋₄ alkyl, alkenyl or alkynyl.
8. A compound as claimed in claim 7, wherein Y stands for an alkylene group.
9. A compound as claimed in any one of claims 1 to 6, wherein R' stands for aryl, preferably phenyl, or a heteroaryl containing up to 3 hetero atoms, or a cycloalkyl or heterocycloalkyl group, each of which may be fused to one or more aryl, heteroaryl, cycloalkyl or heterocycloalkyl rings, each optionally substituted by one or more of alkyl, halide alkyl haloalkyl, alkoxy or haloalkoxy.
10. A compound as claimed in any one of claim 1 or claims 3 to 9, wherein R'' is H, C₁₋₄ alkyl (e.g. methyl, ethyl or propyl), aryl, heteroaryl, cycloalkyl or heterocycloalkyl.
11. A compound as claimed in any one of claims 1 to 10, wherein X is NR⁵, most preferably NH, or a straight chain or branched C₁₋₄ alkylene, e.g. methylene or ethylene;
12. A compound as claimed in any one of claims 1 to 11, wherein Y is either absent or a straight of branched chain C₁₋₄, e.g. methylene or methylmethylene.
13. A compound as claimed in any one of claims 1 to 11, wherein Y is NR⁶, e.g. NH, wherein R⁶ is as defined in claim 1.
14. A compound as claimed in claim 13, wherein X stands for NR⁵ wherein R⁵ is as defined in claim 1.

15. A compound as claimed in any one of claims 1 or 3 to 14, wherein Z is O.

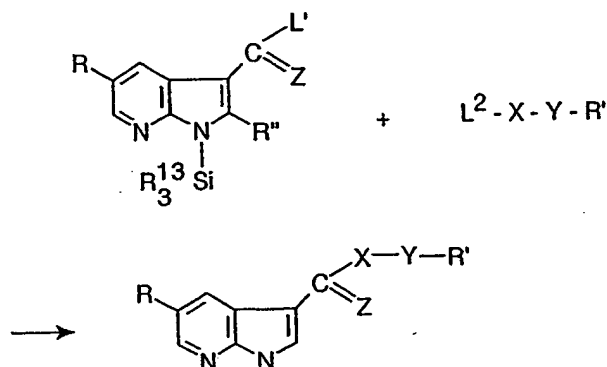
16. A compound as claimed in any one of claims 1 to 15 selected from

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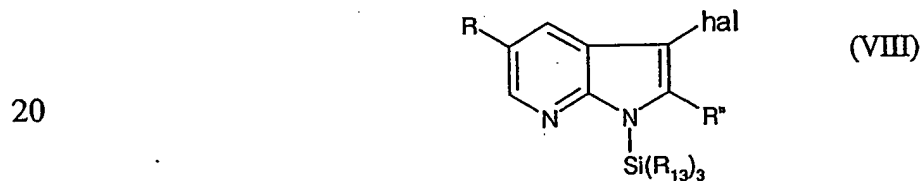
17. A prodrug of a compound as defined in any of claims 1 to 16.

5 18. A process for the manufacture of any one or more of the compounds of any one of claims 1 to 16 which comprises condensing a compound of the general formula (II) with the compound of the general formula (III):



10 in which R, R', R'', X and Y are as defined in any one of claims 1 to 16, Z is O, R¹³ stands for C₁₋₆ straight or branched alkyl and L¹ and L² stand for radicals that together form a condensation product, e.g. H and OH, to form the compound of the general formula (I) or (Ia) as defined in any one of claims 1 to 16, in which Z stands for oxygen.

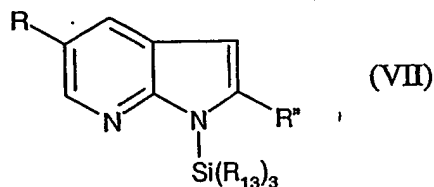
15 19. A process as claimed in claim 18, wherein the compound of the general formula (II) (in which Z stands for O and L¹ stands for OH) is formed by reacting a compound of the general formula (VIII)



25 in which R₁₃, R and R'' are as defined in claim 18 and hal stands for a halogen atom, preferably bromine, with an alkali metal alkyl, e.g. an alkyl lithium such as tertiary butyl lithium, and then reacting the product so obtained with CO₂.

20. A process as claimed in claim 19, wherein the compound of the general formula (VIII) is formed by halogenating (preferably with bromine) the compound of the formula (VII) in the 3 position

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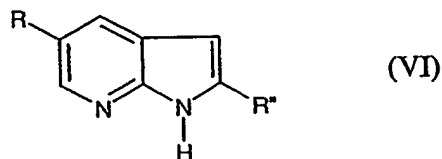


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in which R_{13} , R and R'' are as defined in claim 18.

21. A process as claimed in claim 20, wherein the compound of the general formula (VII) is formed by reacting a compound of the general formula (VI)

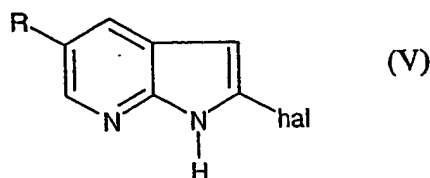
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20 in which R and R'' are as defined in claim 18, with an alkali metal alkyl, e.g. an alkyl lithium such as normal or tertiary butyl lithium, followed by reacting the product so obtained with $R_{13}^3\text{Si-hal}$, in which R_{13} , is as defined in claim 18 and hal stands for a halogen atom.

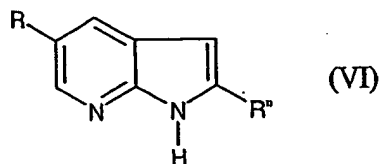
25 22. A process as claimed in claim 20 or 21, wherein the compound of the general formula (VI), in which R'' stands for hydrogen, is formed by hydrogenating a compound of the general formula (V):

30

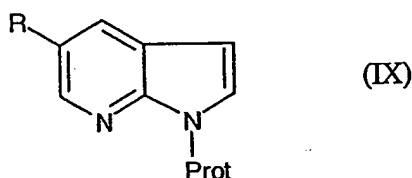


in which R is as defined in claim 18 and hal stands for a halogen atom, e.g. using hydrogen and a catalyst such as Pd-C.

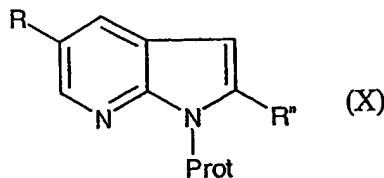
23. A process as claimed in claim 21, wherein the compound of the general formula (VI), in which R'' is as defined in claim 18 except that it does not stand for hydrogen, is formed by protecting the compound of the general formula (VI),



10 in which R'' stands for hydrogen, in the 1 position with a suitable protecting radical, e.g. with an arylsulphonyl group, such as a phenylsulphonyl group, to form a compound of the general formula (IX)

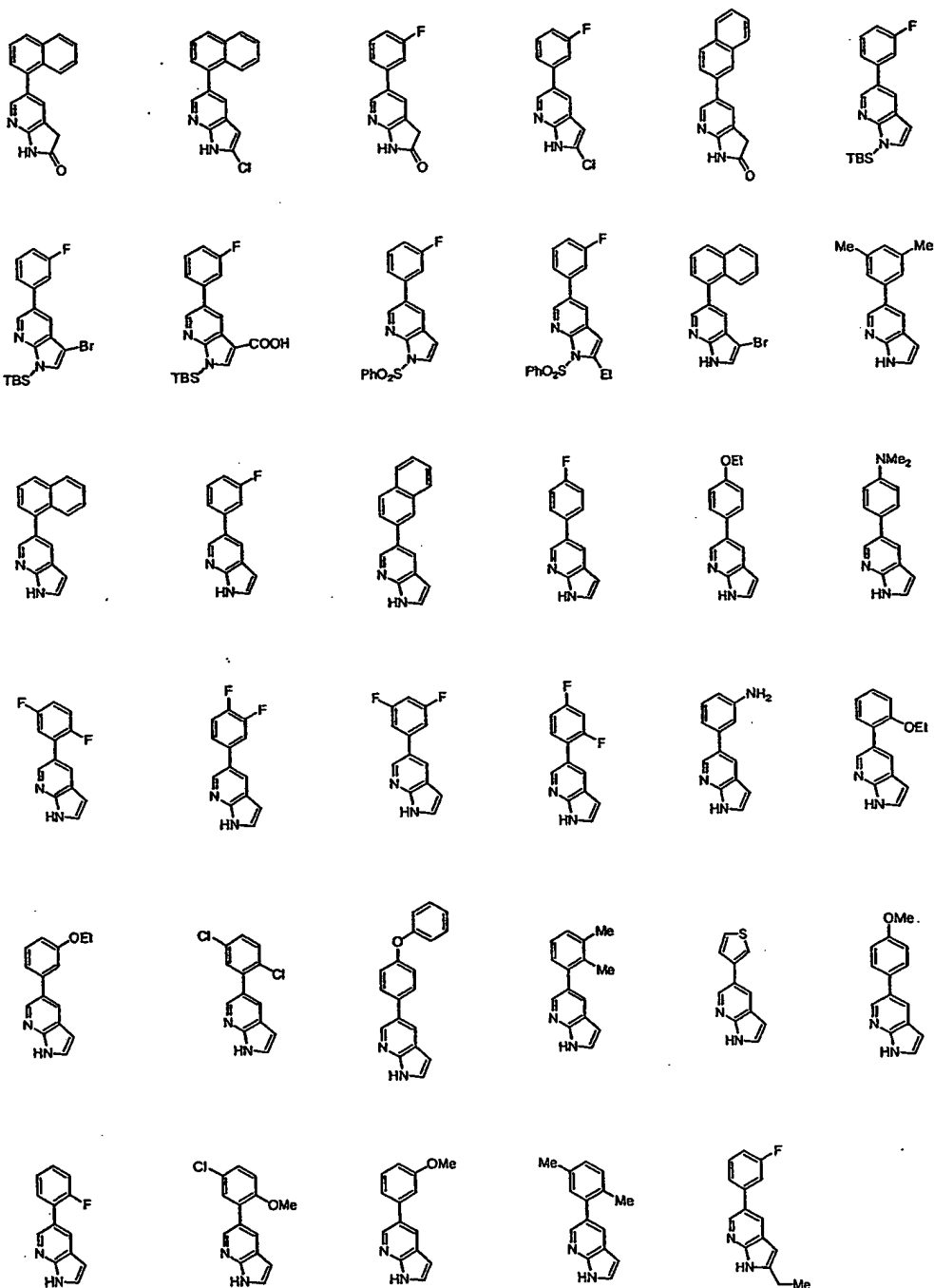


20 in which R is as defined in claim 18 and prot stands for the protecting group, and treating the compound of the general formula (IX) with an alkali metal alkyl, e.g. an alkyl lithium, and then with a compound R''-hal (where hal stands for a halogen, preferably iodine, and R'' is as defined in claim 18 except that it does not stand for hydrogen) to form the compound of the general formula (X)

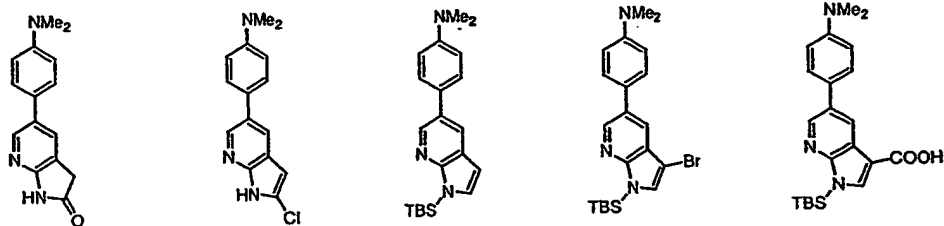


30 in which R and R'' are as defined in claim 18 except that R'' does not stand for hydrogen and in which prot stands for the protecting group, and removing the protecting group, e.g. phenylsulphonyl, to form a compound of the general formula (VI) in which R and R'' are as defined in claim 18 except that R'' does not stand for hydrogen.

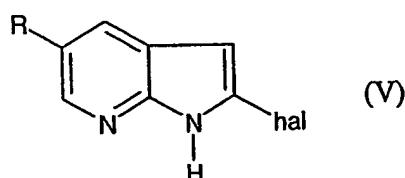
24. A process as claimed in claim 22 or 23, wherein the compound of the general formula (VI) is selected from:



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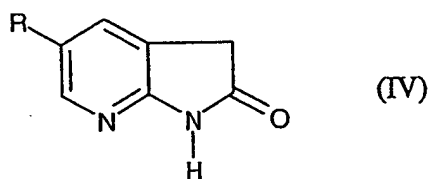


25. A process as claimed in any one of claims 22 to 24, wherein the compound of the general formula (VI), in which R'' stands for hydrogen, is formed by hydrogenating a compound of the general formula (V),



in which R is as defined in claim 18 and hal stands for a halogen atom, e.g. using hydrogen and a catalyst such as Pd-C.

26. A process as claimed in claim 25, wherein the compound of the general formula (V) is formed by halogenating a compound of the general formula (IV) in the 2 position,



in which R is as defined in claim 18.

27. A process as claimed in any one of claims 18 to 26, which includes the further step of converting the compound of the general formula (I) in which Z stands for O into a compound of the general formula (I) in which Z stands for S or NR⁷.

28. A composition comprising a compound as defined in any of claims 1-16 in combination with a pharmaceutically acceptable carrier, diluent or excipient.
29. A composition as claimed in claim 28 further comprising one or more
5 other active agent.
30. A composition as claimed in claim 29 wherein the composition further comprises an anti-inflammatory agent, for example a p38 inhibitor.
- 10 31. A process for the manufacture of a composition as defined in any of claims 28-30, comprising combining a compound as defined in any of claims 1-16, and any additional active agent, with the pharmaceutically acceptable carrier or diluent.
- 15 32. A compound as defined in any of claims 1-16, or a composition as defined in any of claims 28-30, for use in therapy.
33. A compound as defined in any of claims 1-16, or a composition as defined in any of claims 28-30, for inhibiting JNK.
- 20 34. A compound as defined in any of claims 1-16, or a composition as defined in any of claims 28-30, for selectively inhibiting JNK3.
- 25 35. A compound as defined in any of claims 1-16, or a composition as defined in any of claims 28-30, for use in the prevention or treatment of a JNK-mediated disorder.
- 30 36. A compound or a composition as claimed in claim 35, wherein the disorder is a neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, proliferative disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin

induced platelet aggregation and/or any condition associated with prostaglandin endoperoxidase synthase-2.

5 37. A compound or composition as claimed in claim 36, wherein the neurodegenerative disorder results from apoptosis and/or inflammation.

38. A compound or composition as claimed in claim 36 or claim 37, wherein the neurodegenerative disorder is: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; 10 Sydenham's chorea; hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity including glutamate neurotoxicity; cerebral ischemia; dementia linked to meningitis and/or neurosis; 15 cerebrovascular dementia; or dementia in an HIV-infected patient.

39. A compound or composition as claimed in claim 36 or 37, wherein the neurodegenerative disorder is a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy, such as may be 20 found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy 25 secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

40. A compound or composition as claimed in claim 36, wherein the disorder 30 is inflammatory bowel disorder; bronchitis; asthma; acute pancreatitis; chronic pancreatitis; allergies of various types; Alzheimer's disease; autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, glomerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes,

autoimmune haemolytic anaemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.

5 41. A method of treating or preventing a JNK-mediated disorder in an individual, which method comprises administering to said individual a compound as claimed in any of claims 1-16 or a composition as claimed in any of claims 28-30.

10 42. A method as claimed in claim 41, wherein the individual is in need of the treatment or prevention of the disorder.

15 43. A method as claimed in claim 41 or 42, wherein the disorder is a neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, proliferative disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and/or any condition associated with prostaglandin
20 endoperoxidase synthase-2.

44. A method as claimed in claim 43, wherein the neurodegenerative disorder results from apoptosis and/or inflammation.

25 45. A method as claimed in claim 43 or 44, wherein the neurodegenerative disorder is: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea; hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia;
30 glutamate toxicity including glutamate neurotoxicity; cerebral ischemia; dementia linked to meningitis and/or neurosis; cerebrovascular dementia; or dementia in an HIV-infected patient.

46. A method as claimed in claim 43 or 44, wherein the neurodegenerative disorder is a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy, such as may be found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

47. A method as claimed in claim 41, 42 or 43, wherein the disorder is inflammatory bowel disorder; bronchitis; asthma; acute pancreatitis; chronic pancreatitis; allergies of various types; Alzheimer's disease; autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, glomerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytic anaemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.

48. A method as claimed in any of claims 41-47, wherein one or more other active agent is administered to the individual simultaneously, subsequently or sequentially to administering the compound.

49. A method as claimed in claim 48, wherein the other active agent is an anti-inflammatory agent such as a p38 inhibitor.

50. Use of a compound as defined in claim 1-16 in the manufacture of a medicament for the prevention or treatment of a JNK-mediated disorder.

51. Use as claimed in claim 50, wherein the disorder is a neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, proliferative disorder, cancer, infectious disease, allergy, ischemia
5 reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and/or any condition associated with prostaglandin endoperoxidase synthase-2.

52. Use as claimed in claim 51, wherein the neurodegenerative disorder
10 results from apoptosis and/or inflammation.

53. Use as claimed in claim 51 or 52, wherein the neurodegenerative disorder is: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea;
15 hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity including glutamate neurotoxicity; cerebral ischemia; dementia linked to meningitis and/or neurosis; cerebrovascular dementia; or
20 dementia in an HIV-infected patient.

54. Use as claimed in claim 51 or 52, wherein the neurodegenerative disorder is a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy, such as may be found in diabetes mellitus,
25 Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy secondary to sarcoidosis;
30 multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

55. Use as claimed in claim 51, wherein the disorder is inflammatory bowel disorder; bronchitis; asthma; acute pancreatitis; chronic pancreatitis; allergies of various types; Alzheimer's disease; autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, glomerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytic anaemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.
56. Use as claimed in any of claims 50-55, wherein the medicament further includes one or more other active agent.
57. Use as claimed in claim 56, wherein the other active agent is an anti-inflammatory agent such as a p38 inhibitor.
58. An assay for determining the activity of the compounds as defined in any of claims 1-16, comprising providing a system for assaying the activity and assaying the activity of a compound as defined in any of claims 1-16.
59. An assay as claimed in claim 58, wherein the assay is for the JNK inhibiting activity of the compound, preferably for the JNK3-specific inhibiting activity of the compound.
60. An assay as claimed in claim 58 or 59, wherein the assay is a Scintillation Proximity Assay (SPA) using radiolabelled ATP, or is ELISA.
61. A method of inhibiting the activity or function of a JNK, particularly JNK3, which method comprises exposing a JNK to a compound as defined in any of claims 1-16 or a composition as defined in any of claims 28-40.
62. A method as claimed in claim 61, which is performed in a research model.

63. A method as claimed in claim 62, wherein the research model is an animal model.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/01112

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/437 A61P25/16 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | WO 01 47922 A (DEPRETS STEPHANIE; LAI JUSTINE YEUN QUAI (GB); MORLEY ANDREW DAVID) 5 July 2001 (2001-07-05) Abstract; page 158; claims 1-66. | 1-63 |
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

20 May 2003

Date of mailing of the international search report

30/05/2003

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/01112

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | HARPER S J ET AL: "INHIBITORS OF THE JNK SIGNALING PATHWAY" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 26, no. 10, October 2001 (2001-10), pages 957-973, XP008008533 ISSN: 0377-8282 the whole document | 1-63 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,17 (part)

The scope of the claims 1 and 2, in as far as the expressions "pharmaceutically acceptable biohydrolyzable derivatives", "affinity reagents" and "prodrugs" are concerned is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to these expressions. Nevertheless, the search was complete for esters, amides, carbamates, carbonates and ureides of compounds (I).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/01112

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 41-49 and 61-63 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1,17 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/01112

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